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POLG-Related Disorders

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Summary

Clinical characteristics

POLG-related disorders comprise a continuum of overlapping phenotypes that were clinically defined before the molecular basis was known. *POLG*-related disorders can therefore be considered an overlapping spectrum of disease presenting from early childhood to late adulthood. The age of onset broadly correlates with the clinical phenotype.

In individuals with early-onset disease (prior to age 12 years), liver involvement, feeding difficulties, seizures, hypotonia, and muscle weakness are the most common clinical features. This group has the worst prognosis.

In the juvenile/adult-onset form (age 12-40 years), disease is typically characterized by peripheral neuropathy, ataxia, seizures, stroke-like episodes, and, in individuals with longer survival, progressive external ophthalmoplegia (PEO). This group generally has a better prognosis than the early-onset group.

Late-onset disease (after age 40 years) is characterized by ptosis and PEO, with additional features such as peripheral neuropathy, ataxia, and muscle weakness. This group overall has the best prognosis.

Diagnosis/testing

Establishing the diagnosis of a *POLG*-related disorder relies on clinical findings and the identification of biallelic *POLG* pathogenic variants on molecular genetic testing for all phenotypes except autosomal dominant progressive external ophthalmoplegia (adPEO), for which identification of a heterozygous *POLG* pathogenic variant on molecular genetic testing is diagnostic.

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Management

Treatment of manifestations: Clinical management is largely supportive and involves standard approaches for associated complications including occupational, physical, and speech therapy; nutritional support; respiratory support; and standard treatment of liver failure, epilepsy, movement abnormalities, sleep disorders, vision, and hearing issues.

Surveillance: Evaluations by a multidisciplinary team of health care providers based on clinical findings; routine evaluation of growth, nutrition, oral intake, and respiratory status; monitoring of liver enzymes every three months or as clinically indicated; monitoring of epilepsy with repeat liver function tests after introduction of any new anti-seizure medication.

Agents/circumstances to avoid: Valproic acid (Depakene®) and sodium divalproate (divalproex) (Depakote®) because of the risk of precipitating and/or accelerating liver disease.

Genetic counseling

Early-onset and juvenile/adult-onset *POLG*-related disorders are typically caused by biallelic pathogenic variants and inherited in an autosomal recessive manner. Late-onset PEO may be caused by a heterozygous *POLG* pathogenic variant and inherited in an autosomal dominant manner.

Autosomal recessive inheritance: If both parents are known to be heterozygous for a *POLG* 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 *POLG* pathogenic variants. Heterozygous sibs of a proband with an autosomal recessive *POLG*-related disorder are typically asymptomatic. Once the *POLG* pathogenic variants have been identified in an affected family member, testing for at-risk family members is possible.

Autosomal dominant inheritance: Most individuals with PEO caused by a heterozygous *POLG* pathogenic variant (i.e., adPEO) have an affected parent, although age of onset and severity of presentation can vary greatly from generation to generation. Each child of an individual with *POLG*-related adPEO has a 50% chance of inheriting the pathogenic variant.

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

GeneReview Scope

POLG-related disorders encompass a broad range of phenotypes. With the current widespread use of multigene panels and comprehensive genomic testing based on an unbiased (i.e., not phenotype-driven) approach, it has become apparent that (1) *POLG* pathogenic variants are associated with a continuum of features – encompassing and transcending previously defined clinical designations – in which almost any organ system can be involved, and (2) the presenting features in individuals with *POLG*-related disorders cluster by age (e.g., neonates are likely to present with liver involvement, feeding difficulties, and seizures, while adolescents are likely to present with seizure, ataxia, and peripheral neuropathy) [Rahman & Copeland 2019, Hikmat et al 2020].

***POLG*-Related Disorders: Typically Presenting Features by Age**

Age at Onset	Feeding Difficulties	Hypotonia	Liver Involvement	Seizures	Stroke-Like Episodes	Migraine	Ataxia	Peripheral Neuropathy	Limb Weakness	PEO	Ptosis	Selected Clinical Designations
<12 yrs	+++	+	+++	+++	+	+	+	+				AHS MCHS

POLG-Related Disorders: Typically continued from previous page.

Age at Onset	Feeding Difficulties	Hypotonia	Liver Involvement	Seizures	Stroke-Like Episodes	Migraine	Ataxia	Peripheral Neuropathy	Limb Weakness	PEO	Ptosis	Selected Clinical Designations
12-40 yrs			+	+++	+	+	+++	+++	+	+		MEMSA ANS
>40 yrs							+++	+	+	+++	+++	arPEO adPEO

Adapted from Rahman & Copeland [2019] and Hikmat et al [2020]
+++ = feature is typically present; + = feature is often present
adPEO = autosomal dominant progressive external ophthalmoplegia; AHS = Alpers-Huttenlocher syndrome; ANS = ataxia neuropathy spectrum; arPEO = autosomal recessive progressive external ophthalmoplegia; MCHS = myocerebrohepatopathy spectrum; MEMSA = myoclonic epilepsy myopathy sensory ataxia

Diagnosis

Suggestive Findings

POLG-related disorders comprise a continuum of overlapping phenotypes. A *POLG*-related disorder **should be suspected** in individuals with combinations of the following clinical features and laboratory and neuroimaging findings.

Clinical features. Clinical features form a continuum but vary in their age of onset. Apart from progressive external ophthalmoplegia (PEO) / ptosis, other features could present at any time from infancy to adulthood. The most common clinical features by age of onset are:

- **Prior to age 12 years (early-onset disease):**
  - Liver involvement (See Laboratory Findings.)
  - Feeding difficulties
  - Seizures
  - Hypotonia and muscle weakness that can evolve into corticospinal tract dysfunction (spasticity and dystonia)
- **Between age 12 and 40 years (juvenile/adult-onset disease):**
  - Ataxia
  - Peripheral neuropathy
  - Seizures
  - Stroke-like episodes
  - PEO (in individuals with longer survival)
- **After age 40 years (late-onset disease):**
  - Ptosis
  - PEO
  - Ataxia
  - Muscle weakness
- **Other features**
  - Developmental delay, especially in childhood-onset disease
  - Movement disorder (e.g., myoclonus, dysarthria, choreoathetosis, parkinsonism)
  - Myopathy (e.g., proximal > distal limb weakness with fatigue and exercise intolerance)
  - Episodic psychomotor regression
  - Psychiatric illness (e.g., depression, mood disorder), more commonly reported in adult-onset phenotypes

- Endocrinopathy (e.g., premature ovarian failure)

Laboratory findings

- Elevated serum lactate in serum and cerebrospinal fluid (CSF) is common throughout the spectrum of phenotypes but is more common in early-onset disease (however, normal values do not eliminate the likelihood of a *POLG*-related disorder).
- CSF protein levels are generally elevated in individuals with Alpers-Huttenlocher syndrome (AHS) and other *POLG*-related disorders, but absence of this finding does not exclude a *POLG*-related disorder.
- Evidence of liver dysfunction or failure can be present, which may occur following exposure to certain anti-seizure medications. This could result in elevation of liver enzymes (alanine transaminase, aspartate transaminase, and gamma-glutamyl transferase) as well as synthetic liver dysfunction, causing hypoglycemia, hyperammonemia, elevated glutamine, hyperbilirubinemia, prolonged bleeding times (international normalized ratio, prothrombin time, partial thromboplastin time), hypoalbuminemia, and low cholesterol levels.
- Respiratory chain defect and/or a defect of mitochondrial DNA (mtDNA) (depletion or multiple deletions) can be present. This could result in respiratory chain dysfunction, identified by either enzymatic assays or polarographic assays. Depletion of mtDNA can be measured by comparing mtDNA to nuclear DNA content in an affected tissue (e.g., liver). Normal respiratory chain function or absence of mtDNA depletion does not rule out a *POLG*-related disorder.
- In muscle biopsy samples, ragged-red fibers, COX-negative fibers, excessive lipid deposits, and abnormal respiratory chain activities can be present. However, biochemical findings on muscle biopsy can be normal.

Neuroimaging features

- Brain computerized tomography (CT) or magnetic resonance imaging (MRI) may be normal early in the course of AHS.
- As AHS evolves, neuroimaging shows gliosis (initially more pronounced in occipital lobe regions) and generalized brain atrophy. These findings are also reported in some individuals with adult-onset *POLG*-related disorders.
- Cortical focal lesions manifesting as T_2/FLAIR hyperintensities in cortical and subcortical areas can be seen. These findings are typical in AHS but have also been reported in sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) and ataxia neuropathy spectrum (ANS) [Parada-Garza et al 2020, García-Cabo et al 2023].

Other diagnostic studies

- Abnormal epileptiform activity over the occipital lobes in individuals with epilepsy
- Abnormal nerve conduction studies (NCVs)

Establishing the Diagnosis

The diagnosis of most *POLG*-related disorders **is established** in a proband by identification of **biallelic** pathogenic (or likely pathogenic) variants in *POLG* by molecular genetic testing (see Table 1). The diagnosis of autosomal dominant progressive external ophthalmoplegia (adPEO) **is established** in a proband by identification of a **heterozygous** pathogenic (or likely pathogenic) variant in *POLG* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview*

is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene 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

Single-gene testing. Sequence analysis of *POLG* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. 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 intragenic and whole-gene deletions or duplications.

Note: (1) In individuals with a suspected autosomal recessive *POLG*-related disorder but in whom only one *POLG* pathogenic variant has been identified by single-gene testing, identification of a second in *trans* pathogenic variant in *POLG*, use of RNA sequencing of *POLG*, or identification of pathogenic variants in other genes known to be associated with the phenotype may be revealing. (2) Sequence analysis of *TWNK* (formerly *C10orf2* or *PEO1*) may be considered in persons with a suspected autosomal recessive *POLG*-related disorder but in whom only one *POLG* pathogenic variant has been identified by single-gene testing, to investigate the possibility of digenic inheritance (see Differential Diagnosis). Digenic inheritance has been reported in PEO in two individuals with pathogenic variants in *POLG* and *TWNK* [Van Goethem et al 2003a, Da Pozzo et al 2015]. (3) In the 5% of simplex cases of PEO in which only a single pathogenic variant is identified, it can be difficult to distinguish between autosomal recessive inheritance and autosomal dominant inheritance caused by a *de novo* *POLG* pathogenic variant.

A multigene panel that includes *POLG*, *TWNK* (formerly *C10orf2* or *PEO1*), and other genes of interest (see Differential Diagnosis) may 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

Comprehensive genomic testing including exome sequencing, mtDNA sequencing, and genome sequencing may be considered.

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 *POLG*-Related Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
POLG	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Ashley et al [2008], Hunter et al [2011], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. 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. Compton et al [2011], Naess et al [2012], Rouzier et al [2014], Lin et al [2021]

Clinical Characteristics

Clinical Description

POLG-related disorders comprise a continuum of broad and overlapping phenotypes that range from fatal neonatal-onset disease to mild late-onset disease with myopathy and progressive external ophthalmoplegia (PEO).

Although some affected individuals present with one of the clinical entities caused by *POLG* pathogenic variants, many have some, but not all, of the features of one or more of the recognized phenotypes. Although clinical phenotypes in affected individuals from the same family are often similar, ages of onset, specific features, and rate of progression may differ. *POLG*-related disorders can therefore be considered an overlapping spectrum of disease presenting from early childhood to late adulthood. The age of onset broadly correlates with the clinical phenotype [Rahman & Copeland 2019, Hikmat et al 2020]. Table 2 summarizes the clinical findings in *POLG*-related disorders.

Table 2. Clinical Findings in *POLG*-Related Disorders

System	Manifestation	% of Persons w/Manifestation
Neurologic	Epilepsy (incl myoclonic, focal motor & generalized seizures, status epilepticus, & epilepsia partialis continua)	~70%
	Tone abnormalities (most commonly hypotonia)	~50%
	"Cerebrovascular" involvement (incl migraines & stroke-like episodes)	~36%
	Movement disorder (incl extrapyramidal movement disorders such as parkinsonism & chorea, & cerebellar ataxia)	~60%
	Peripheral neuropathy (sensory neuronopathy / ganglionopathy & axonal sensorimotor neuropathy [1])	~53%
	Headache (migraine-like)	~36%

Table 2. continued from previous page.

System	Manifestation	% of Persons w/Manifestation
Gastrointestinal	Liver issues (most notably liver failure that is either spontaneous or precipitated by valproic acid or sodium divalproate in children)	~64%
	Gastrointestinal dysmotility (incl vomiting, diarrhea, & feeding difficulties)	~6%-52%
Ophthalmologic	Cataracts	~7%
	Ptosis & external ophthalmoplegia	~34%-38%
	Cortical blindness	~30%
	Retinopathy	~2%
Audiologic	Sensorineural hearing loss	~11%
Neuromuscular/ myopathy	Proximal or distal myopathy	~70%
	Exercise intolerance	Common in adolescence & adult-onset phenotypes
Endocrine	Primary ovarian failure & ovarian dysgenesis	Rare
	Primary testicular failure	Rare
	Diabetes mellitus	~1%
Renal	Renal tubular acidosis, renal failure, renal stones	~11% (MCHS)
Respiratory	Ventilatory Weakness (muscle, nerve, central respiratory drive)	~12%

Based on Hudson & Chinnery [2006], Chow et al [2017], Hikmat et al [2017b], Rahman & Copeland [2019], and Hikmat et al [2020]
MCHS = childhood myocerebrohepatopathy spectrum
1. Corresponds to the acronym SANDO (sensory ataxia neuropathy dysarthria and ophthalmoplegia)

Early-Onset Disease (Prior to Age 12 Years)

Typical features of early-onset *POLG*-related disorders (prior to age 12 years) include liver involvement, feeding difficulties, seizures, hypotonia and muscle weakness. Prognosis is usually the worst of the three age-related groups. Phenotypes that typically occur include Alpers-Huttenlocher syndrome and childhood myocerebrohepatopathy spectrum.

Alpers-Huttenlocher Syndrome (AHS)

AHS, one of the most severe phenotypic manifestations in the *POLG*-related spectrum, is characterized by progressive and severe encephalopathy with intractable epilepsy, neuropathy, and liver failure. While AHS is usually fatal, age of onset, rate of neurologic deterioration, presence of liver failure, and age of death vary among affected individuals [Davidzon et al 2006, Nguyen et al 2006, Wong et al 2008, Cohen & Naviaux 2010, Saneto et al 2013, Hikmat et al 2020]. Children with AHS appear healthy at birth and may develop normally over the first few weeks to years of life. Some have variable degrees of developmental delay prior to the initial recognition of neurodegeneration. Onset is usually between ages two and four years but ranges overall from one month to 36 years.

Seizures are the first sign of AHS in about 50% of affected children. Seizures may be simple focal, primary generalized, or myoclonic. The most common early seizure types are partial seizures and secondary generalized tonic-clonic seizures. In some children, the first seizure presents with status epilepticus. EEG findings include high-amplitude slow activity with smaller polyspikes or intermittent continuous spike-wave activity [Hikmat et al 2017a].

In some instances, the initial seizure type is epilepsia partialis continua (EPC), a classic motor seizure type that involves only one portion of the body (e.g., a limb) with constant and repetitive myoclonic jerking, continuing for hours or days with or without dramatic effects on consciousness. EPC is not always apparent as an abnormality on EEG and can be mistaken for a conversion reaction. EEG may be normal or show only focal slowing of the background rhythm.

Over time, seizures can evolve into a complex epileptic disorder such as focal status epilepticus, EPC, or multifocal myoclonic epilepsy [Horvath et al 2006, Tzoulis et al 2006, Hikmat et al 2017a].

In some children, seizures are initially controllable with standard dosages of anti-seizure medications (ASM); in others, seizures, such as EPC, are refractory from the onset. Over time, seizures become increasingly resistant to ASMs. (See Treatment of Manifestations for further information about management of seizures.)

Of note, valproic acid (Depakene®) and sodium divalproate (divalproex) (Depakote®) can precipitate liver dysfunction in individuals with AHS and should be avoided. These medications are considered absolutely contraindicated in individuals with *POLG*-related disorders [Saneto et al 2010] (see Agents/Circumstances to Avoid).

Headaches, another common first presenting symptom, are typically associated with visual sensations or visual auras that reflect early occipital lobe dysfunction and have features similar to migraines [Hakonen et al 2005, Tzoulis et al 2006, Hikmat et al 2020]. **Stroke and stroke-like episodes** may occur as well [Horvath et al 2006].

Movement disorders, primarily myoclonus and choreoathetosis, are common [Horvath et al 2006]. Myoclonus can be difficult to distinguish from myoclonic seizures and EPC. Palatal myoclonus resulting from involvement of the inferior olivary nuclei can be seen as well. Some individuals develop parkinsonism, which may temporarily respond to levodopa [Luoma et al 2004, Mancuso et al 2004] (see Treatment of Manifestations).

Neuropathy and ataxia develop in all persons with AHS unless the disease process is so rapid that it results in early death. All neurologic signs and symptoms, including ataxia and nystagmus, may worsen during infections or with other physiologic stressors.

Areflexia (resulting from neuropathy) and **hypotonia** (possibly the result of generalized weakness as part of systemic illness or pyramidal or extrapyramidal dysfunction) are often both present early in the disease course.

Episodic psychomotor regression is variably present at the time of initial consideration of the diagnosis. The major motor manifestation is a progressive spastic paraparesis resulting from progressive loss of cortical neuronal function. Progressive spasticity occurs universally, has variable onset, and evolves over months to years.

Loss of cognitive function occurs throughout the course of the disease, but the time of onset and rate of progression are variable. Significant sudden or rapid regression is often seen during infectious illnesses. The clinical manifestations may include somnolence, loss of concentration, loss of language skills (both receptive and expressive), irritability with loss of normal emotional responses, and memory deficits. In addition to cognitive impairment caused by refractory epilepsy, high dosages of ASMs can lead to significant cognitive dysfunction. Therefore, the degree of cognitive dysfunction is often difficult to assess due to frequent seizures and high therapeutic doses of ASMs.

Vision loss leading to blindness may appear months to years after the onset of other neurologic manifestations. Retinopathy (see Retinitis Pigmentosa) may also play a less important role in vision loss [Hakonen et al 2005, Hikmat et al 2020]. **Hearing loss** is variable [Hakonen et al 2005, Horvath et al 2006].

Liver involvement can progress rapidly to end-stage liver failure within a few months, although this is highly variable. End-stage liver disease is often heralded by hypoalbuminemia and prolonged coagulation time, followed shortly thereafter by fasting hypoglycemia and hyperammonemia. Rapid-onset liver failure has been described when valproic acid (Depakene®) and sodium divalproate (divalproex) (Depakote®) have been used to

treat seizures, although the introduction of other ASMs, including phenytoin, may also play a role in onset of hepatic failure (see Agents/Circumstances to Avoid).

Disease progression is variable in timing and rapidity. Loss of neurologic function culminates in dementia, spastic quadriparesis from corticospinal tract involvement, visual loss, and death. The rate of neurodegeneration varies and is marked by periods of stability. The typical life expectancy from onset of first symptoms ranges from three months to 12 years.

Neuroimaging. CT or MRI of the brain may be normal early in the course of AHS. As the illness evolves, neuroimaging shows gliosis (initially more pronounced in the occipital lobe regions) and generalized cortical atrophy. Restricted diffusion unilaterally in the pulvinar and occipital region is described in the acute phase. FLAIR and T_2-weighted sequence images demonstrate high signal intensity in deep gray matter nuclei, especially in the thalamus and cerebellum [Alves et al 2018]. Progressive cerebellar atrophy can occur in addition to cortical atrophy. The pons, midbrain, and globus pallidum can also be involved. Lesions described in the inferior olivary nuclei may also be a part of AHS and are associated with palatal myoclonus. Brain magnetic resonance spectroscopy (MRS) typically shows reduced N-acetylaspartate, normal creatine, and lactate.

Histopathologic abnormalities

- **Brain.** The gross appearance of the brain varies from normal to severe atrophy, depending on the state of disease progression. Central nervous system regions affected in AHS are the same as those affected by Leigh syndrome but typically evolve in the reverse order. For example, in AHS, gliosis is most severe and occurs earliest in the cerebral cortex, followed by the cerebellum, basal ganglia, and brain stem. Involved regions demonstrate neuronal degeneration, characteristic spongiform or microcystic degeneration, and – as seen in Leigh syndrome – gliosis, necrosis, and capillary proliferation. The cortical ribbon shows patchy lesions, but the calcarine cortex, which is characteristically involved early in the course of the disease, is usually narrowed, granular, and discolored.

  Microscopic abnormalities throughout the cerebral cortex evolve as the disease progresses. Early in the course of the disease, spongiosis, astrocytosis, and neuronal loss are prevalent in the superficial cortex. Later, the deeper laminae are affected. In the most advanced stages, the entire cortex becomes a thin dense gliotic scar. Usually, the striate cortex is the most affected part of the brain, followed by the thalamus, hippocampus, and cerebellum. These pathologic features differ from those resulting from hypoxic injury, recurrent seizures, or other causes of hepatic failure.

- **Liver.** Liver histology may demonstrate macro- and microvesicular steatosis, centrilobular necrosis, disorganization of the normal lobular architecture, hepatocyte loss with or without bridging fibrosis or cirrhosis, regenerative nodules, bile duct proliferation, or mitochondrial proliferation with a vivid eosinophilic cytoplasm. Florid cirrhosis occurs late in the disease. This pathology differs from that seen in chemically induced or toxic hepatopathies.

Childhood Myocerebrohepatopathy Spectrum (MCHS)

MCHS presents between the first few months of life through age three years. In one study, it presented at a median age of 4.7 months (range: 0.9-7 months) with developmental delay or dementia, lactic acidosis, myopathy/hypotonia, and failure to thrive.

Other features that may be present include liver failure, renal tubular acidosis, pancreatitis, cyclic vomiting, and hearing loss. Seizures occur in about 75% of affected individuals. This is an ultimately fatal illness with a median age of death in one study of 15.8 months (range: 1.0-184.6 months). Major causes of death include liver failure, sepsis, and status epilepticus [Wong et al 2008, Hikmat et a 2017b, Rahman & Copeland 2019].

Juvenile/Adult-Onset Disease (Age 12-40 Years)

Typical features of juvenile/adult-onset *POLG*-related disorders (age 12-40 years) include peripheral neuropathy, ataxia, seizures, stroke-like episodes, and, in individuals with longer survival, progressive external ophthalmoplegia (PEO). Prognosis is usually better than in the early-onset group. Phenotypes that typically occur include myoclonic epilepsy myopathy sensory ataxia and ataxia neuropathy spectrum.

Myoclonic Epilepsy Myopathy Sensory Ataxia (MEMSA)

Previously referred to as spinocerebellar ataxia with epilepsy (SCAE), MEMSA describes the spectrum of disorders presenting with myopathy, epilepsy, and ataxia without ophthalmoplegia. Cerebellar ataxia, generally the first sign, begins in young adulthood as a subclinical sensory polyneuropathy. Epilepsy develops in later years, often beginning focally and then spreading to become generalized. As in other *POLG*-related phenotypes, seizures may be refractory to medical therapy. Recurrent seizures are accompanied by progressive interictal encephalopathy. The myopathy in MEMSA may be distal or proximal, and, as in other *POLG*-related disorders, it may also present as exercise intolerance.

Ataxia Neuropathy Spectrum (ANS)

ANS includes mitochondrial recessive ataxia syndrome (MIRAS) and a separate entity known as sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) [Fadic et al 1997]. ANS is characterized by ataxia, neuropathy, and (in most but not all affected individuals) encephalopathy with seizures. The encephalopathy is similar to that seen in AHS but tends to be more slowly progressive and can even be mild. The neuropathy may be sensory, motor, or mixed and can be severe enough to contribute to ataxia – so-called sensory ataxia. About 25% of affected individuals have cramps, but clinical myopathy is less common and, if present, is not the main component of issues pertaining to gait dysfunction or balance difficulties.

Other features include myoclonus, blindness, and liver dysfunction [Wong et al 2008]. Liver findings range from no dysfunction, to elevated enzymes and mild synthetic dysfunction, to florid liver failure in some cases [Tzoulis et al 2006, Wong et al 2008]. Psychiatric illness including depression is common. Headaches, generally migraines, are also common and may precede other symptoms by many years.

Although muscle pathology may show COX-negative fibers, there may be no pathologic findings.

Late-Onset Disease (Age >40 Years)

Typical features of late-onset *POLG*-related disorders (age >40 years) include ptosis and PEO, with additional features such as peripheral neuropathy ataxia and muscle weakness. Prognosis is usually the best of the three age-related groups. Phenotypes that typically occur include autosomal recessive PEO and autosomal dominant PEO.

Autosomal Recessive Progressive External Ophthalmoplegia (arPEO)

Progressive PEO without systemic involvement is the hallmark of arPEO. Caution needs to be exercised, however, when making the diagnosis of arPEO, as some *POLG* pathogenic variants associated with arPEO are also associated with ANS and other *POLG*-related disorders with systemic involvement. Thus, many individuals who have no other clinical findings at the time of diagnosis with isolated arPEO develop other manifestations of *POLG*-related disorders over subsequent years or decades [Van Goethem et al 2001, Lamantea et al 2002, Van Goethem et al 2003b].

Autosomal Dominant Progressive External Ophthalmoplegia (adPEO)

The universal manifestation of this adult-onset disorder is progressive weakness of the extraocular eye muscles resulting in ptosis and strabismus [Van Goethem et al 2001]. A generalized myopathy is present in most affected

individuals, leading to early fatigue and exercise intolerance. Some affected individuals have variable degrees of sensorineural hearing loss, axonal neuropathy, ataxia, depression, parkinsonism, hypogonadism, and cataracts [Luoma et al 2004, Pagnamenta et al 2006]. Cardiomyopathy and gastrointestinal dysmotility are less common.

Rare Phenotypes

POLG pathogenic variants have been shown to be associated with Charcot-Marie-Tooth neuropathy type 2 [Harrower et al 2008, Phillips et al 2019], Leigh syndrome [Naess et al 2009, Taanman et al 2009], and a MNGIE-like illness [Tang et al 2012].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

In a study of 155 individuals with *POLG*-related disorders in which the age of onset of features was analyzed by median age rather than age range, Hikmat et al [2020] observed that age of onset broadly correlates with clinical phenotype (see *GeneReview* Scope) and prognosis. Based on this observation, Hikmat et al [2020] proposed the following system of classification that differs from the classic descriptions of *POLG*-related phenotypes and provides alternate nomenclature:

- **Early-onset disease** refers to individuals with onset prior to age 12 years. This classification encompasses Alpers-Huttenlocher syndrome (AHS) and childhood myocerebrohepatopathy spectrum (MCHS) and is associated with the worst prognosis.
- **Juvenile/adult-onset disease** refers to individuals with onset at age 12-40 years. This classification encompasses myoclonic epilepsy myopathy sensory ataxia (MEMSA) / spinocerebellar ataxia with epilepsy (SCAE) and ataxia neuropathy spectrum (ANS) and generally has a better prognosis than the early-onset disease group.
- **Late-onset disease** refers to individuals with onset after age 40 years. This classification encompasses autosomal recessive progressive external ophthalmoplegia (arPEO), autosomal dominant progressive external ophthalmoplegia (adPEO), and progressive external ophthalmoplegia plus (PEO-plus) and has the best prognosis overall.

Prevalence

AHS is reported to affect approximately 1:51,000 people [Darin et al 2001].

The combined frequency of the most common autosomal recessive pathogenic variants in *POLG* can be used to estimate disease frequency at 1:10,000. Common *POLG* variants include those in Table 3.

Table 3. Frequency of the Most Common *POLG* Pathogenic Variants

POLG Pathogenic Variant	Prevalence	Reference
p.Ala467Thr	0.6% (Belgian)	Van Goethem et al [2001]
	0.17%-0.69% (European)	Horvath et al [2006]
	0.69% (United Kingdom)	Craig et al [2007]
	0% (Italian)	Craig et al [2007]
p.Trp748Ser	0.8% (Finnish)	Hakonen et al [2005]
	0% (Italian)	Craig et al [2007]
p.Gly848Ser	0.016% (likely European)	Hakonen et al [2007], Nurminen et al [2017]

Table 3. continued from previous page.

POLG Pathogenic Variant	Prevalence	Reference
p.[Thr251Ile;Pro587Leu] [1]	1% (Italian)	Ferrari et al [2005], Scuderi et al [2015]

Based on Rahman & Copeland [2019]; see also Table 8
1. Indicates two different pathogenic variants in *cis* (see varnomen.hgvs.org)

Pathogenic variants in *POLG*, identified in nearly 50% of individuals with adPEO in one study [Lamantea et al 2002], may be the most frequent cause of adPEO.

Genetically Related (Allelic) Disorders

To date, no phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *POLG*.

Differential Diagnosis

Table 4. Genes of Interest in the Differential Diagnosis of *POLG*-Related Disorders

Gene(s) [1] / Genetic Mechanism	Disorder	MOI	Comment
ALDH7A1	Pyridoxine-dependent epilepsy – *ALDH7A1* (pyridoxine-dependent epilepsy)	AR	• Neonatal-onset progressive encephalopathy w/ refractory seizures • Targeted therapy: seizures are not well controlled w/ASMs but respond to large daily supplements of pyridoxine (vitamin B_6).
AMT *GLDC*	Nonketotic hyperglycinemia (NKH)	AR	Epilepsia partialis continua has been described in some affected persons. [2]
ATP7A	Menkes disease (See *ATP7A*-Related Copper Transport Disorders.)	XL	• Neonatal-onset progressive encephalopathy w/ refractory seizures • Usually present earlier in infancy than AHS
BCS1L	*BCS1L*-related disorders (incl GRACILE syndrome [OMIM 603358], Bjørnstad syndrome [OMIM 262000], & GRACILE syndrome-Bjørnstad syndrome overlap phenotype]	AR	The clinical scenario of a hepatoencephalopathy may appear similar to AHS at a single point in time, but mtDNA depletion is not part of the pathology described in those w/*BCS1L* pathogenic variants.
BTD	Biotinidase deficiency	AR	• Neonatal-onset progressive encephalopathy w/ refractory seizures • Targeted therapy: Oral biotin. Compliance w/ biotin therapy can prevent development of disease & also improves symptoms in symptomatic persons.
CACNA1A	*CACNA1A*-related early infantile epileptic encephalopathy (OMIM 617106)	AD	Severe infantile epileptic disorder that appears progressive at onset but usually plateaus into developmental arrest/delay
CACNB4	Idiopathic generalized epilepsy & myoclonic epilepsy (OMIM 607682) & episodic ataxia type 5 (OMIM 613855)	AD	Early-onset epileptic disorder that is often assoc w/ myoclonic, generalized tonic-clonic, or absence seizures w/photosensitivity reported in some persons [3]

Table 4. continued from previous page.

Gene(s) [1] / Genetic Mechanism	Disorder	MOI	Comment
CERS1 *CSTB* *EPM2A* *GOSR2* *KCNC1* *KCTD7* *LMNB2* *NHLRC1* *PRDM8* *PRICKLE1* *SCARB2* *SEMA6B* *SLC7A6OS*	Myoclonic epilepsy (OMIM PS254800)	AR AD	Can cause dementia or pseudodementia because of unrelenting seizures & anticonvulsant side effects
CLN5 *CLN6* *CLN8* *PPT1* *TPP1*	CLN1 disease & CLN2 disease (neuronal ceroid lipofuscinoses [NCLs]) (OMIM PS256730)	AR	Phenotypes incl in NCLs that overlap w/AHS are CLN1 disease, classic infantile (previously classic infantile NCL, INCL, Santavuori-Haltia) & CLN2 disease, classic late infantile (previously late-infantile NCL, LINCL, Jansky-Bielschowsky disease)
COQ8A	*COQ8A*-related primary coenzyme Q_{10} (CoQ_{10}) deficiency	AR	• Epilepsia partialis continua has been described in some affected persons. [4] • Targeted therapy: Persons w/primary CoQ_{10} deficiency may respond well to high-dose oral CoQ_{10} supplementation.
CTSA	Galactosialidosis (OMIM 256540)	AR	During infancy & early childhood, storage diseases can be assoc w/progressive encephalopathy w/primary involvement of cortical gray matter & refractory epilepsy.
DGUOK	Deoxyguanosine kinase deficiency (DGUOK deficiency)	AR	In contrast to *POLG*-related AHS, DGUOK deficiency is not characterized by seizures or brain imaging abnormalities.
DNA2	*DNA2*-related mtDNA maintenance defect	AD	PEO & PEO w/systemic involvement [5]
FBXL4	*FBXL4*-related encephalomyopathic mtDNA depletion syndrome	AR	Early infantile encephalopathy, hypotonia, lactic acidosis, & mtDNA depletion [6]
FOLR1	*FOLR1*-related cerebral folate transport deficiency	AR	• Neonatal-onset progressive encephalopathy w/ refractory seizures • Targeted therapy: Oral administration of 5-formylTHF is usually sufficient to bring CSF folate levels into normal range for age.
HEXA	Hexosaminidase A deficiency	AR	During infancy & early childhood, storage diseases can be assoc w/progressive encephalopathy w/primary involvement of cortical gray matter & refractory epilepsy.
HEXB	Sandhoff disease	AR	
MGME1	*MGME1*-related mtDNA maintenance defect	AR	Multisystemic mitochondrial phenotype w/PEO, emaciation, & respiratory failure
MPV17	*MPV17*-related mtDNA maintenance defect	AR	Multisystemic mitochondrial disease w/liver dysfunction, brain & peripheral nerve disease, gastrointestinal dysmotility, & lactic acidosis

Table 4. continued from previous page.

Gene(s) [1] / Genetic Mechanism	Disorder	MOI	Comment
MT-TK [7]	MERFF [8]	See footnote 9.	• Multisystemic mitochondrial disorder characterized by myoclonus (often 1st symptom) followed by generalized epilepsy, ataxia, weakness, exercise intolerance, & dementia • Onset can occur from childhood to adulthood, following normal early development • Common findings are ptosis, hearing loss, short stature, optic atrophy, cardiomyopathy, cardiac dysrhythmias, & peripheral neuropathy
MT-TL1 [10]	MELAS [8, 11]	See footnote 12.	• Multisystemic mitochondrial disorder w/onset typically occurring in childhood • Onset of symptoms is often ages 2-10 yrs. • Most common initial symptoms are generalized tonic-clonic seizures, recurrent headaches, anorexia, & recurrent vomiting. • Seizures are often assoc w/stroke-like episodes of transient hemiparesis or cortical blindness. The cumulative residual effects of the stroke-like episodes gradually impair motor abilities, vision, & mentation by adolescence or young adulthood. • Sensorineural hearing loss is common.
NDUFS4	NADH coenzyme Q reductase deficiency (OMIM 252010)	AR	Epilepsia partialis continua has been described in some affected persons. [13]
NEU1	Infantile sialidosis (OMIM 256550)	AR	During infancy & early childhood, storage diseases can be assoc w/progressive encephalopathy w/primary involvement of cortical gray matter & refractory epilepsy.
OPA1	Optic atrophy type 1 (OMIM 165500)	AD	Childhood-onset visual loss
PABPN1	Oculopharyngeal muscular dystrophy	AD	Progressive adult-onset myopathy w/ ptosis, dysphagia, & proximal weakness
PLPBP	PLPBP deficiency (pyridoxine-dependent epilepsy)	AR	• Neonatal-onset progressive encephalopathy w/ refractory seizures • Targeted therapy: Pyridoxine is the first-line therapy. Most individuals have a favorable response to pyridoxine.
PNPO	PNPO deficiency (pyridoxine-dependent epilepsy)	AR	• Neonatal-onset progressive encephalopathy w/ refractory seizures • Targeted therapy: ~60% of persons are resistant to pyridoxine & require treatment with pyridoxal 5'-phosphate; ~40% respond to pyridoxine alone.
POLG2	*POLG2*-related mtDNA maintenance defect	AD	Adult-onset PEO & multisystemic mitochondrial disease w/mtDNA depletion
RNASEH1	*RNASEH1*-related mtDNA maintenance defect	AR	PEO & multisystemic mitochondrial disease w/ mtDNA depletion

Table 4. continued from previous page.

Gene(s) [1] / Genetic Mechanism	Disorder	MOI	Comment
RRM2B	*RRM2B* mtDNA maintenance defects	AR AD	• Neonatal-onset hypotonia, lactic acidosis, & neurologic deterioration, w/ or w/o renal tubular dysfunction • Adult-onset PEO, variable gastrointestinal dysmotility, multisystemic mitochondrial disease
SCN1A	*SCN1A* seizure disorders	AD	At the severe end of the spectrum, severe infantile epileptic disorder that appears progressive at onset but usually plateaus into developmental arrest/delay
SCN2A	*SCN2A*-related early infantile epileptic encephalopathy (OMIM 613721)	AD	Severe infantile epileptic disorder that appears progressive at onset but usually plateaus into developmental arrest/delay
SCO1	*SCO1*-related disorders (OMIM 603644)	AR	Infantile-onset multisystemic mitochondrial disease, Leigh-like syndrome w/cardiac hypertrophy & failure
SLC25A19	*SLC25A19*-related thiamine metabolism dysfunction (incl Amish lethal microcephaly & thiamine metabolism dysfunction syndrome 4)	AR	Targeted therapy: Oral thiamine treatment is critical from the time of diagnosis. This treatment is lifelong. It prevents metabolic decompensation & improves outcomes.
SLC25A4	*SLC25A4*-related mtDNA maintenance defect	AR	Primary presenting features are myopathy, hypertrophic cardiomyopathy, & ophthalmoplegia.
SLC46A1	Hereditary folate malabsorption	AR	• Neonatal-onset progressive encephalopathy w/ refractory seizures • Targeted therapy: Early treatment w/oral 5-formylTHF or, preferably, the active isomer of 5-formylTHF (Isovorin® or Fusilev®) readily corrects the systemic folate deficiency &, if the dose is sufficient, can achieve CSF folate levels that prevent or mitigate the neurologic consequences of hereditary folate malabsorption.
SUCLA2	*SUCLA2*-related mtDNA depletion syndrome, encephalomyopathic form w/ methylmalonic aciduria	AR	Infantile encephalomyopathy, methylmalonic aciduria, epilepsy, hepatopathy, & cardiomyopathy
SUCLG1	*SUCLG1*-related mtDNA depletion syndrome, encephalomyopathic form w/ methylmalonic aciduria [14]	AR	
SUOX	Isolated sulfite oxidase deficiency	AR	• Neonatal-onset progressive encephalopathy w/ refractory seizures • Usually present earlier in infancy than AHS
TBC1D24	*TBC1D24*-related disorders	AR [15]	Epilepsia partialis continua has been described in some affected persons. [2]
TK2	*TK2*-related mtDNA maintenance defect, myopathic form	AR	At the severe end of the spectrum, infantile-onset myopathy w/neurologic involvement & rapid progression to early death

Table 4. continued from previous page.

Gene(s) [1] / Genetic Mechanism	Disorder	MOI	Comment
TWNK	Autosomal dominant PEO, infantile-onset spinocerebellar ataxia, Perrault syndrome, & *TWNK*-related mtDNA maintenance defect [16]	AR AD	Digenic inheritance of PEO has been reported in 2 persons w/double heterozygosity for a *POLG* pathogenic variant & a *TWNK* pathogenic variant. [17]
TYMP	Mitochondrial neurogastrointestinal encephalopathy	AR	Cachexia, gastrointestinal dysmotility, peripheral neuropathy, PEO, leukoencephalopathy [18]

Table 4. continued from previous page.

Gene(s) [1] / Genetic Mechanism	Disorder	MOI	Comment
Single large-scale mitochondrial DNA deletion ranging in size from 1.1 to 10 kb	Chronic progressive external ophthalmoplegia (CPEO) & Kearns-Sayre syndrome (KSS) (See Single Large-Scale Mitochondrial DNA Deletion Syndromes.)	See footnote 19.	• CPEO in a simplex case or when there is a maternal family history can be the result of a large-scale single deletion of mtDNA that may only be detected in limited tissues (e.g., skeletal muscle). CPEO is sometimes complicated by mild proximal muscle weakness & dysphagia & can be considered to lie on a spectrum of disease from pure CPEO to KSS. [20] • A multisystemic disorder defined by the triad of onset age <20 years, pigmentary retinopathy, & PEO. In addition, persons have ≥1 of the following: cardiac conduction block, CSF protein concentration >100 mg/dL, or cerebellar ataxia. Onset is usually in childhood. PEO, characterized by ptosis, paralysis of the extraocular muscles (ophthalmoplegia), & variably severe proximal limb weakness, is relatively benign. [21]

5-formytetrahydrofolate = 5-formylTHF; AD = autosomal dominant; AHS = Alpers-Huttenlocher syndrome; AR = autosomal recessive; ASM = anti-seizure medication; CSF = cerebrospinal fluid; GRACILE syndrome = *g*rowth *r*estriction, *a*minoaciduria, *c*holestasis, *i*ron overload, *l*actic acidosis, and *e*arly death syndrome; MOI = mode of inheritance; PEO = progressive external ophthalmoplegia; XL = X-linked

1. Genes are ordered alphabetically.

2. Mameniškienė & Wolf [2017]

3. Amadori et al [2022]

4. Hikmat et al [2016]

5. Ronchi et al [2013]

6. Gai et al [2013]

7. The m.8344A>G pathogenic variant in the mitochondrial gene *MT-TK* is present in more than 80% of affected individuals with typical findings. Pathogenic variants in *MT-TF*, *MT-TH*, *MT-TI*, *MT-TL1*, *MT-TP*, *MT-TS1*, and *MT-TS2* have also been described in a subset of individuals with MERRF.

8. Evidence to date suggests that diabetes and cardiomyopathy are not common in *POLG*-related disorders, distinguishing *POLG*-related disorders from other multisystemic mitochondrial diseases.

9. MERRF is caused by pathogenic variants in mtDNA and is transmitted by maternal inheritance.

10. The m.3243A>G pathogenic variant in the mitochondrial gene *MT-TL1* is present in approximately 80% of individuals with MELAS. Pathogenic variants in *MT-TL1* or other mtDNA genes, particularly *MT-ND5*, can also cause this disorder

11. Hirano et al [1992]

12. MELAS is caused by pathogenic variants in mtDNA and is transmitted by maternal inheritance.

13. Antozzi et al [1995]

14. Molaei Ramsheh et al [2020]

15. Most *TBC1D24*-related disorders are inherited in an autosomal recessive manner.

16. Peter & Falkenberg [2020]

17. Van Goethem et al [2003a], Da Pozzo et al [2015]

18. Pacitti et al [2018]

19. SLSMDSs are almost never inherited, suggesting that these disorders are typically caused by a *de novo* single large-scale mitochondrial DNA deletion (SLSMD) that occurs in the mother's oocytes during germline development or in the embryo during embryogenesis.

20. Some individuals with CPEO (<20%) have a pathogenic single-nucleotide variant of mtDNA (e.g., m.3243A>G).

21. Most individuals with KSS have a common deletion of 4,977 nucleotides involving 12 mitochondrial genes.

Other Disorders to Consider

Leigh syndrome is a progressive neurodegenerative disorder characterized by hypotonia, spasticity, dystonia, muscle weakness, hypo- or hyperreflexia, seizures, movement disorders, cerebellar ataxia, and peripheral

neuropathy. In individuals with Leigh syndrome, MRI changes most often occur initially in the brain stem, and the gliosis "migrates" over time to involve the deep gray masses and cortex, whereas in AHS the initial lesions form in the cerebral cortex (usually the occipital lobes), followed by the cerebellum, basal ganglia, thalamus, and brain stem. Epilepsia partialis continua (EPC), seen in Alpers-Huttenlocher syndrome (AHS), has been described in individuals with Leigh syndrome [Mameniškienė & Wolf 2017]. Most individuals with Leigh syndrome have an autosomal recessive or X-linked disorder of mitochondrial energy generation (see Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview); Leigh syndrome can also be caused by genetic alternations in mitochondrial DNA (see Mitochondrial DNA-Associated Leigh Syndrome and NARP and Single Large-Scale Mitochondrial DNA Deletion Syndromes).

For additional disorders to consider in the differential diagnosis of individuals presenting with **ataxia**, see Hereditary Ataxia Overview.

For additional disorders to consider in the differential diagnosis of individuals presenting with **peripheral neuropathy**, see Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Management

No clinical practice guidelines for *POLG*-related disorders have been published, although consensus statement guidelines for primary mitochondrial diseases are available [Parikh et al 2017].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *POLG*-related disorder, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to diagnosis) are recommended. Evaluation should always include measures of functional neurologic status.

Table 5. *POLG*-Related Disorders: Recommended Evaluations Following Initial Diagnosis

System	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI [1] • Consider EEG & video EEG if seizures are a concern.
Ataxia	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education, need for speech therapy
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD. Formal neuropsychological eval can be considered for those w/any concerns identified on screening.
	Depression screen	Assess for mood disturbances.

Table 5. continued from previous page.

System	Evaluation	Comment
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Consideration of exercise program
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl liver function tests incl ALT & AST; serum concentrations of ammonia, glutamine & tyrosine, bilirubin, albumin, & cholesterol; fasting blood glucose levels; & coagulation factors (prothrombin time or INR) [2] • Consideration of liver ultrasound to evaluate for liver fibrosis • To incl eval of aspiration risk incl swallow study for bulbar symptoms & nutritional status • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings (e.g., cataract, retinal dystrophy) that may require referral for subspecialty care &/or low vision services
Hearing	Audiologic eval	Assess for hearing loss.
ENT/Mouth	ENT eval	A sleep study is recommended to evaluate for central or obstructive apnea or hypopnea that results in either pCO_2 elevation or O_2 desaturation.
Cardiovascular	Cardiac eval	To incl echocardiogram & electrocardiogram
Respiratory	Pulmonary eval	To incl baseline pulmonary function testing
Endocrine	Screen for pancreatic, thyroid, & adrenal function.	Consider if clinically indicated & in critical illness. [3]
Pregnancy	High-risk obstetrical care	To incl discussion between managing physicians
Genetic counseling	By genetics professionals [4]	To inform affected persons & their families re nature, MOI, & implications of *POLG*-related disorders to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ALT = alanine transaminase; ASD = autism spectrum disorder; AST = aspartate aminotransferase; INR = international normalized ratio; MOI = mode of inheritance; OT = occupational therapy; pCO_2: partial pressure of carbon dioxide; PT = physical therapy

1. In some instances, the first neuroimaging study may be normal, but with certain phenotypes, such as Alpers-Huttenlocher syndrome, changes may be seen in a relatively short amount of time.

2. AST elevation, and to a lesser extent ALT elevation, may be due to muscle disease. Therefore, simultaneously obtaining a serum CK level helps differentiate between liver & muscle involvement, which can both be seen in individuals with *POLG*-related disorders.

3. Parikh et al [2017]

4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *POLG*-related disorders. 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 6).

Table 6. *POLG*-related disorders: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	OT, PT, & ST are indicated in AHS to maintain or improve neurologic function for as long as possible & for comfort care.
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Note: Valproic acid (Depakene®) & sodium divalproate (divalproex) (Depakote®) should be avoided (see Agents/Circumstances to Avoid). Because other ASMs may also accelerate liver deterioration, it is reasonable to monitor liver enzymes every 2-4 weeks after introducing any new ASM. • Treatment of epilepsy is similar to non-mitochondrial disease w/seizures. Lamotrigine may worsen myoclonic seizures. [1] Vigabatrin may need to be avoided in persons w/mtDNA depletion because it inhibits conversion of deoxyribonucleoside diphosphate to deoxyribonucleoside triphosphate in the mitochondrial nucleoside salvage pathway & may worsen mtDNA depletion. [2] Topiramate may worsen acidosis. [3] • Refractory epilepsy, esp EPC, may be impossible to control w/any treatment. In persons w/EPC, use of high-dose ASM may control the clinical seizures, but assoc obtundation & subsequent risk of aspiration & ventilatory failure may outweigh the benefit. • Education of parents/caregivers [4]
Movement disorders	Standard treatment by an experienced neurologist	• Myoclonus & other non-epileptic movement disorders occur as part of AHS. The use of benzodiazepines often ↓ severity of abnormal movements & also assists in seizure control & reduction of spasticity. • Chorea & athetosis may cause pain, & treatment w/muscle relaxants & pain medications, incl narcotics, is advised. Some movement disorders can be treated w/dopaminergic medication such as levodopa-carbidopa or tetrabenazine; a trial of either of these medications can be considered. [5]
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	• Consider need for positioning & mobility devices, disability parking placard. • Botulinum toxin can be used w/caution (w/consideration of systemic effects). [6]
Inadequate weight gain & linear growth (children) or unexplained weight loss (all ages)	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	• Low threshold for renal eval in persons w/inadequate weight gain & linear growth or unexplained weight loss • A feeding eval &/or radiographic swallowing study should be considered when showing clinical signs or symptoms of dysphagia.
GI & bowel dysfunction	Standard treatment by GI specialist for feeding or nutritional issues	Placement of a gastric feeding tube when appropriate can maintain nutritional status &/or prevent aspiration.
	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Liver failure	Standard treatment	• Treatment may incl small, frequent meals or continuous feeding to compensate for defective gluconeogenesis; reduction in dietary protein; use of non-absorbable sugars to create an osmotic diarrhea; & use of conjugating agents to treat hyperammonemia. • Levocarnitine may have some benefit in the setting of liver failure & has a low risk, yet there is no evidence for routine use.
Eyes	Standardized treatment by ophthalmologist	For refractive errors, strabismus, & more complex findings (e.g., cataract, retinal dystrophy)
	Ptosis	Surgery for ptosis may provide symptomatic relief for some persons.
	Low vision services	• Children: through early intervention programs &/or school district • Adults: low vision clinic &/or community vision services / OT / mobility services
Cerebral visual impairment	No specific treatment	Consideration of referral to a low vision clinic
Hearing	Hearing aids may be helpful per otolaryngologist	Community hearing services through early intervention or school district
Respiratory	Standard treatment by pulmonologist for respiratory issues	• Tracheostomy placement & artificial ventilation may be performed as needed. • Assessment of nocturnal ventilatory function can be performed for evidence of central &/or obstructive apnea using polysomnography w/measurement of pCO_2 & monitoring by pulse oximetry. Treatment w/CPAP, BiPAP, or more invasive ventilatory therapy as indicated.
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 (esp for persons w/AHS) • Consider involvement in adaptive sports or Special Olympics.

AHS = Alpers-Huttenlocher syndrome; ASM = anti-seizure medication; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; EPC = epilepsia partialis continua; OT = occupational therapy; PT = physical therapy; ST = speech therapy
1. Hikmat et al [2017a]
2. Besse et al [2015]
3. Mirza et al [2011]
4. 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.
5. Hakonen et al [2005]
6. Parikh et al [2017]

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 and hearing 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 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.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior 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, evaluations by a multidisciplinary team including neurologist, biochemical geneticist, hepatologist or gastroenterologist, physiatrist, psychiatrist, neuropsychologist and/or psychologist, ophthalmologist, and pulmonologist are recommended. No standard-of-care guidelines regarding the recommended frequency of evaluations exist; surveillance should be guided by clinical features, and the schedule should be modified if the clinical course is stable. For those with the most severe phenotypes, the recommendations in Table 7 can be considered.

Table 7. *POLG*-related disorders: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders. • EEG & video EEG monitoring (e.g., for suspicion of subclinical status epilepticus or EPC, to determine if events are seizures or non-epileptic movements)	At each visit
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Assessment for anxiety, ADHD, ASD, aggression, & depression	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Liver function & metabolic status	• Complete blood count • Electrolytes • Liver enzymes (AST, ALT, GGT) • CK level • Liver function tests incl preprandial serum glucose level; serum concentration of ammonia, albumin, bilirubin (free & conjugated), & cholesterol; coagulation factors incl prothrombin time or INR	Every 3 mos, or as clinically indicated
	• Urine analysis • Lactic acid levels • Liver ultrasound	Annually or as clinically indicated
	• Plasma amino acids • Plasma concentration of free & total carnitine (unless treated w/levocarnitine, in which case measure annually)	
Gastrointestinal	Monitor for swallowing dysfunction through barium swallow study, gastrointestinal paresis, constipation, feeding intolerance, or malabsorption.	At each visit or as clinically indicated
Respiratory	Monitor for evidence of aspiration & respiratory insufficiency.	At each visit
	Polysomnogram w/CPAP titration as part of an eval of subacute mental status changes, apnea, or snoring	As clinically indicated or every 2-3 yrs
Auditory	Audiogram or brain stem auditory evoked responses	As clinically indicated
Ophthalmologic involvement	Routine ophthalmologic exam	Per treating ophthalmologist(s)
	Low vision services	Per treating clinicians
Cardiovascular	Routine cardiac exam	At each visit
Endocrine	Laboratory testing for thyroid or adrenal dysfunction	Upon critical illness or as clinically indicated
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

ADHD = attention-deficit/hyperactivity disorder; ALT = alanine transaminase; ASD = autism spectrum disorder; AST = aspartate transaminase; CK = creatine kinase; EPC = epilepsia partialis continua; GGT = gamma-glutamyl transferase; INR = international normalized ratio; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Valproic acid (Depakene®) and sodium divalproate (divalproex) (Depakote®) should be avoided because of the risk of precipitating and/or accelerating liver disease [Saneto et al 2010].

As with some other mitochondrial diseases, physical stressors such as infection, fever, dehydration, and anorexia can result in a sudden deterioration and should be avoided if possible.

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 information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Liver transplantation is not advised in children with Alpers-Huttenlocher syndrome (AHS) because transplanting the liver does not alter the rapid progression of the brain disease [Kelly 2000].

However, liver transplantation in adults who have an acceptable quality of life may be of benefit.

- In one report, one of two individuals undergoing liver transplantation survived [Tzoulis et al 2006]. In another report of solid organ transplantation in primary mitochondrial disease, of six individuals with *POLG*-related disease, two survived without complications [Parikh et al 2016].
- In another report, a woman underwent liver transplantation at age 19 years, eight years after experiencing fulminant hepatic failure following onset of valproate therapy. Molecular genetic testing seven years after her liver transplantation confirmed the diagnosis of a *POLG*-related disorder; her phenotype fit best with SANDO [Wong et al 2008, Parikh et al 2016].

The use of other treatments for refractory epilepsy, such as corticotropin or prednisone, ketogenic diet, and intravenous immunoglobulin G, are unproven in the treatment of AHS. The following, however, may be considered:

- Vitamin and cofactor therapy with the intent to fortify mitochondrial function may be offered, yet there is insufficient evidence demonstrating objective benefit in cohorts of persons. There have not been formal studies of the use of these vitamins and cofactors in AHS or other *POLG*-related disorders [Parikh et al 2009, Parikh et al 2015, Camp et al 2016].
- The use of folinic acid should be considered [Hasselmann et al 2010].
- The use of levoarginine has been reported to be helpful in reducing the frequency and severity of the strokes associated with MELAS, and can be considered for use in persons with *POLG*-related disorders, especially if deficiency in the plasma or cerebrospinal fluid arginine concentration is confirmed [El-Hattab et al 2017].
- The use of levocarnitine should be reserved for individuals with reduced free carnitine levels in the blood, and the levels should be monitored [Parikh et al 2015].
- Creatine monohydrate, coenzyme Q_{10}, B vitamins, and antioxidants such as alpha-lipoic acid, vitamin E, and vitamin C have been used as mitochondrial supplements based on limited case reports and small series but with a lack of objective evidence based on randomized controlled trials. Use of all in *POLG*-related disorders is reasonable given the general lack of toxicity but is not mandatory [Gold & Cohen 2001, Rodriguez et al 2007, Horvath et al 2008, Parikh et al 2013, Parikh et al 2015].

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

Early-onset and juvenile/adult-onset *POLG*-related disorders are typically caused by biallelic pathogenic variants and inherited in an autosomal recessive manner. Late-onset progressive external ophthalmoplegia (PEO) may be caused by a heterozygous *POLG* pathogenic variant and inherited in an autosomal dominant manner.

Note: Digenic inheritance involving pathogenic variants in *POLG* and *TWNK* has been reported in two individuals with PEO [Van Goethem et al 2003a, Da Pozzo et al 2015].

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *POLG* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *POLG* 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 [Chan et al 2009, Lutz et al 2009] 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 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.
- Heterozygous parents of a child with an autosomal recessive *POLG*-related disorder are typically asymptomatic.

Sibs of a proband

- If both parents are known to be heterozygous for a *POLG* 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 *POLG* pathogenic variants.
- The *POLG*-related phenotype is usually similar in affected family members; less commonly, affected sibs may present differently in terms of age of onset, specific clinical features, and severity. For example, in a family in which affected sibs were compound heterozygotes (*POLG* pathogenic variants p.Gly848Ser and p.Trp748Ser), one sib presented with developmental delays and status epilepticus at age three years, while the other sib presented with ataxia and myoclonus in early adolescence [Tang et al 2011].
- Heterozygous sibs of a proband with an autosomal recessive *POLG*-related disorder are typically asymptomatic.

Offspring of a proband

- Unless an affected individual's reproductive partner also has *POLG*-related pathogenic variant(s), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *POLG* (see **Family planning**).
- Individuals with early-onset *POLG*-related disorders (e.g., Alpers-Huttenlocher syndrome and childhood myocerebrohepatopathy spectrum) are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a *POLG* pathogenic variant.

Carrier (heterozygote) detection. Carrier testing for at-risk relatives requires prior identification of the *POLG* pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals with PEO caused by a heterozygous *POLG* pathogenic variant (i.e., autosomal dominant PEO or adPEO) have an affected parent, although age of onset and severity of presentation can vary greatly from generation to generation.
- Some individuals diagnosed with adPEO have the disorder as the result of a *de novo POLG* pathogenic variant. The proportion of probands who have a *de novo* pathogenic variant is unknown but thought to be low (<1%).
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the evaluation of the parents include molecular genetic testing for the *POLG* pathogenic variant identified in the proband, a complete family history, and physical examination focusing on the most common features of *POLG*-related disease (ophthalmoplegia, myopathy, ataxia, and neuropathy). Note: Because migraine, depression, gastrointestinal problems, fatigue, exercise intolerance, and seizures are common in the general population, their presence as isolated findings is not likely to be relevant.
- 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.
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation, failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. 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 pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. The *POLG*-related phenotype is generally similar in affected family members, although the age of onset can vary significantly. Data on penetrance of adPEO are not available.
- If the *POLG* pathogenic variant is not detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *POLG* pathogenic variant but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for adPEO because of the possibility of late onset in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *POLG*-related adPEO has a 50% chance of inheriting the *POLG* pathogenic variant.

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

Related Genetic Counseling Issues

At-risk family members. Sibs who are close in age to or younger than the proband may still be at risk and in need of diagnostic evaluation. Note: Because the age of onset, even among family members with identical *POLG* pathogenic variants, can vary considerably, there is no firm certainty as to how many years need to pass before there is no longer a risk of *POLG*-related features in a sib [Rahman & Copeland 2019].

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 at risk of having a *POLG* pathogenic variant.
- Carrier testing should be considered for the reproductive partners of individuals known to have a *POLG* pathogenic variant, particularly if consanguinity is likely and/or if both partners are of the same ancestry.

Prenatal Testing and Preimplantation Genetic Testing

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

- **The PolG Foundation**
  polgfoundation.org
- **American Epilepsy Society**
  aesnet.org
- **Children's Liver Disease Foundation**
  United Kingdom
  Phone: +44 (0) 121 212 3839
  Email: info@childliverdisease.org
  childliverdisease.org
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **MitoAction**

Phone: 888-648-6228
Email: support@mitoaction.org
mitoaction.org

- **Mitochondrial Care Network**
  www.mitonetwork.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Email: naf@ataxia.org
  ataxia.org
- **The Charlie Gard Foundation**
  United Kingdom
  Email: hello@thecharliegardfoundation.org
  www.thecharliegardfoundation.org
- **The Lily Foundation**
  United Kingdom
  Email: liz@thelilyfoundation.org.uk
  www.thelilyfoundation.org.uk
- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **mitoSHARE: UMDF's Patient-Driven Registry**
  www.umdf.org/mitoshare
- **RDCRN Patient Contact Registry: North American Mitochondrial Disease Consortium**
  Patient Contact Registry

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. POLG-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
POLG	15q26.1	DNA polymerase subunit gamma-1	POLG database Human DNA Polymerase Gamma Mutation Database	POLG	POLG

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 POLG-Related Disorders (View All in OMIM)

157640	PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT 1; PEOA1
174763	POLYMERASE, DNA, GAMMA; POLG

Table B. continued from previous page.

203700	MITOCHONDRIAL DNA DEPLETION SYNDROME 4A (ALPERS TYPE); MTDPS4A
258450	PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL RECESSIVE 1; PEOB1
607459	SENSORY ATAXIC NEUROPATHY, DYSARTHRIA, AND OPHTHALMOPARESIS; SANDO
613662	MITOCHONDRIAL DNA DEPLETION SYNDROME 4B (MNGIE TYPE); MTDPS4B

Molecular Pathogenesis

The mitochondrion comprises almost 1,500 proteins, but only the 13 that comprise small portions of the respiratory chain complexes I, III, IV, and V are encoded by the mitochondrial genome. The mitochondrial genome is a circular molecule that in humans contains 15,569 base pairs including 37 genes – 13 genes encoding for subunits of complexes I, III, IV, and V, as well as 22 tRNAs and 2 rRNAs – that are distinct and necessary for mitochondrial translation. The terminal portion of energy production occurs in the respiratory chain; disruption of the production and/or assembly of any component leads to a deficiency of ATP and resultant cellular energy failure. The cause of clinical symptoms likely includes insufficient ATP production, but also excessive free radical production, disturbed calcium handling, and other factors. Unlike nuclear DNA, mitochondrial DNA (mtDNA) replicates continuously and independently of cell division. Polymerase (pol) gamma is the major DNA polymerase in humans required for replication and repair of mtDNA. Replication of mtDNA requires a heterotrimer of one catalytic subunit of pol gamma and two accessory subunits, encoded by *POLG2*, that assist in binding and processing the synthesized DNA. The twinkle protein, encoded by *TWNK*, functions as the 5' → 3' DNA helicase.

POLG encodes DNA pol gamma, which has three functional domains:

- Exonuclease, responsible for proofreading (first third of the protein)
- Linker region (center of the protein)
- Polymerase, responsible for replication (last third of the protein)

The clinical features *POLG*-related disorders most likely result from mtDNA depletion or multiple mtDNA deletions [Lujan et al 2020] over time of normal mtDNA, with resultant reduced electron transport chain activity. The adPEO-causing pathogenic variants cluster in the active site region of the DNA polymerase.

Mechanism of disease causation. Loss of *POLG* function results in loss of polymerase activity – resulting in loss of mtDNA – or loss of endonuclease function – resulting in non-fidelity of mtDNA replication – or both. The loss of mtDNA results in loss of normal mitochondrial translation as well as loss of function involving mtDNA-encoded subunits found in complexes I, III, IV, and V. The result is loss of normal ATP production and elevated free radical production and other mitochondrial functions, with resultant injury to neurons and other cells.

Table 8. *POLG* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002693.3 NP_002684.1	c.695G>A	p.Arg232His	Pathogenic variant that when in *trans* w/the p.[Trp748Ser;p.Glu1143Gly] haplotype causes AHS
	c.1399G>A	p.Ala467Thr	Common pathogenic variant in *POLG*-related disorders; severely ↓ DNA polymerase (pol) gamma activity (4% of wild type pol gamma activity) by ↓ affinity for dNTPs & lowering catalytic activity [Chan et al 2005].

Table 8. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	c.1760C>T	p.Pro587Leu	Common pathogenic variant; nearly always occurs w/ p.Thr251Ile in *cis* (i.e., p.[Thr251Ile;Pro587Leu]) in affected persons & in general population. Individually, these variants cause an approximately 30% reduction in DNA polymerase activity, but together there is a synergistic impairment of polymerase function to levels about 5% of normal [DeBalsi et al 2017].
	c.2243G>C	p.Trp748Ser	Common pathogenic variant that causes AHS, ANS, arPEO, & ataxia-neuropathy. Results in ↓ DNA polymerase activity, low processivity, & severe DNA binding defect, but normal POLG2 interactions [Chan et al 2006]. Note: (1) The p.Glu1143Gly variant in *cis* modulates the deleterious effect of p.Trp748Ser by partially rescuing activity & ↓ protein stability [Chan et al 2006]. AHS results when the p.[Trp748Ser;p.Glu1143Gly] haplotype occurs in *trans* with a different pathogenic variant on the other allele (e.g., p.Arg232His). (2) This pathogenic variant is a Finnish founder variant.
	c.2542G>A	p.Gly848Ser	Common pathogenic variant that results in <1% polymerase activity & a defect in DNA binding function [Kasiviswanathan et al 2009]

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.
AHS = Alpers-Huttenlocher syndrome; ANS = ataxia neuropathy spectrum; arPEO = autosomal recessive progressive external ophthalmoplegia; dNTP = deoxyribonucleotide triphosphate

An up-to-date listing of all pathogenic variants is available at tools.niehs.nih.gov, managed by William Copeland, PhD.

Chapter Notes

Author Notes

Bruce H Cohen is a clinician caring for children and adults with mitochondrial disease since his training starting four decades ago. He first began caring for patients with *POLG* disease ten years before the *POLG* gene was cloned and characterized by Dr Copeland and has followed the work of the coauthors over the last 25 years. He has lectured hundreds of times to medical audiences and families on the topic of mitochondrial medicine. For the last decade his focus has been on clinical trials for mitochondrial disease.

Web pages: Google Scholar and Akron Children's

William C Copeland is a biochemist studying mitochondrial DNA replication. He has been leading the Mitochondrial DNA Replication group at the National Institute of Environmental Health Sciences for more than 30 years and is currently the Chief of the Genome Integrity and Structural Biology Laboratory. He uses biochemistry, enzyme kinetics, structural biology, and genetics to study the consequences of *POLG* pathogenic variants.

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Patrick F Chinnery is a neurologist and clinician-scientist caring for adults with mitochondrial disorders. He runs a laboratory and clinical research group studying disease mechanisms and developing new treatments for mitochondrial disorders based at the MRC Mitochondrial Biology Unit and Department of Clinical Neurosciences, University of Cambridge, United Kingdome.

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Bruce Cohen (bcohen@akronchildrens.org) and Patrick Chinnery (pfc25@cam.ac.uk) are actively involved in clinical research regarding individuals with *POLG*-related disorders. They would be happy to communicate with persons who have any questions regarding diagnosis of *POLG*-related disorders or other considerations.

Bruce Cohen (bcohen@akronchildrens.org), Patrick Chinnery (pfc25@cam.ac.uk), and Bill Copeland (copelan1@niehs.nih.gov) are also interested in hearing from clinicians treating families affected by mitochondrial disorders in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Bill Copeland (copelan1@niehs.nih.gov) to inquire about review of *POLG* variants of uncertain significance.

The Mitochondrial Medicine Society (MMS) represents an international group of physicians, researchers, and clinicians working toward advancing education, research, and global collaboration in clinical mitochondrial medicine. Information about the MMS and educational resources can be found at www.mitosoc.org.

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