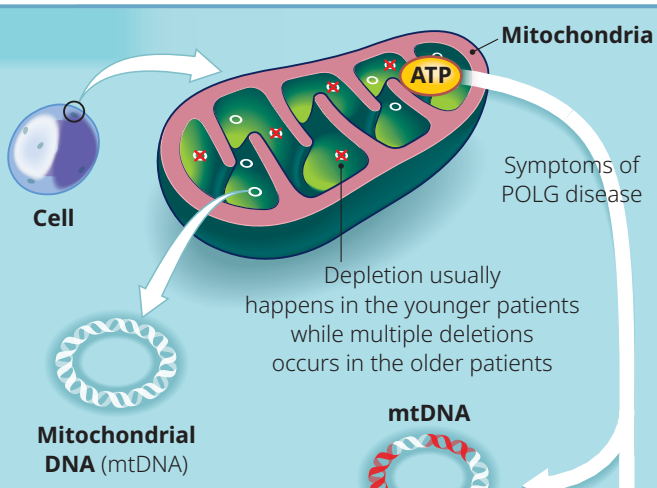
POLG Disease: A Clinical Reference Guide

What is POLG disease ?

POLG disease is a spectrum of rare mitochondrial disorders caused by mutations in the POLG gene. This gene encodes the DNA polymerase gamma complex, essential for mitochondrial DNA (mtDNA) replication and repair.

The replication of mtDNA relies on **polymerase gamma** (POLG) complex, an enzyme encoded by the POLG and POLG2 genes in the nucleus.

Mutations in these genes disrupt mtDNA replication, leading to mtDNA depletion or multiple deletions, and ultimately result in impaired energy production. This energy failure can affect multiple organ systems.



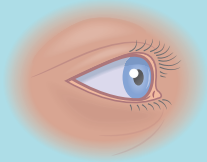
Epidemiology

The true prevalence of POLG-related disease is likely underestimated, as it is often underdiagnosed due to its highly variable clinical presentation, even among people with the same mutation.

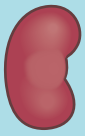
The estimated birth prevalence is approximately 1:10,000[1]

Both autosomal recessive and autosomal dominant inheritance patterns exist, although autosomal dominant forms are rare and typically mutation-specific.

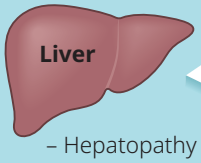
[1]Cohen BH et al. *POLG-Related Disorders*. GeneReviews®, University of Washington, Seattle; 2024.56



Eye
– Ptosis
– Ophthalmoplegia
– Cataracts
– Cortical vision impairment



Kidney
– Fanconi's syndrome
– Tubulopathy



Liver
– Hepatopathy
– Coagulopathy

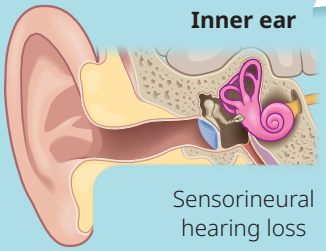
Symptoms and clinical presentation

Symptoms affect predominantly parts of the body that are particularly energy-hungry such as the central nervous system, muscles, and liver. Children often present with more severe and early-onset forms of POLG-related disease.

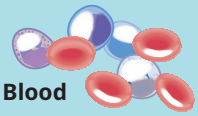
Progression is often rapid, especially in pediatric forms.

Genotype–phenotype patterns in POLG are observed and grouped in five functional clusters, yet variability hinders absolute outcome prediction.

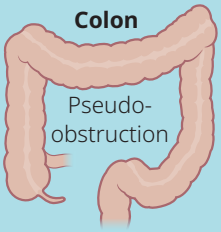
(See mitomap.org/polg and Rahman S et al. *POLG-related disorders*. Nat Rev Neurol. 2019)



Inner ear
Sensorineural hearing loss



Blood
Anemia



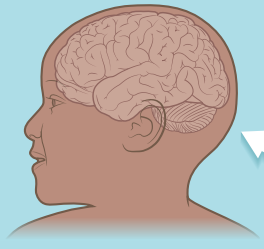
Colon
Pseudo-obstruction

Most common clinical characteristics

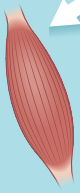
Onset prior to 12 years of age – Liver involvement, seizures, feeding difficulties, hypotonia, developmental delay.

Onset between 12 and 40 years – Ataxia, peripheral neuropathy, seizures.

Onset over 40 years – Ptosis, progressive external ophthalmoplegia, ataxia.



Brain
– Seizures
– Myoclonus
– Ataxia
– Stroke-like episodes
– Dementia
– Migraine



Skeletal muscle
– Weakness
– Fatigue
– Myopathy
– Neuropathy
– Exercise intolerance

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Diagnosis challenges

POLG is often missed or misdiagnosed for a number of reasons, including its highly variable clinical presentation, low clinical awareness, and non-specific test results.

POLG is often misdiagnosed as unexplained epilepsy, and unexplained liver failure.

In cases presenting with seizures, it may be mistaken for conditions such as NORSE (new-onset refractory status epilepticus), FIRES (febrile infection-related epilepsy syndrome), or autoimmune encephalitis. When peripheral neuropathy is prominent, misdiagnoses may include Charcot-Marie-Tooth disease (CMT) or chronic inflammatory demyelinating polyneuropathy (CIDP).

Red flags for POLG referral

Consider POLG testing in cases of rapidly progressive neurological and liver symptoms, especially in children with seizures and acute liver failure.

In adults, unexplained ataxia and peripheral neuropathy without an identifiable cause should raise suspicion for POLG-related disease. In addition, new-onset status epilepticus, particularly in females around puberty or during pregnancy, may also be a clinical clue.

Treatment and management

There is currently no cure for POLG, but supportive care can help:

- Seizure control (but avoid valproate – **toxic in POLG!**)
- Immunomodulatory treatments
- Liver monitoring (N-acetylcysteine for liver failure)
- Physical/occupational therapy and diet

Advocacy and support

There are critical unmet needs in the POLG community:

- Faster diagnosis remains a top priority; raising awareness among neurologists and pediatricians can prevent harmful delays and reduce the risk of mismanagement (such as inappropriate medication use)
- Funding is urgently needed to support POLG-specific clinical trials and accelerate the path from research to treatment

Advocacy, awareness, and collaboration are key to driving progress

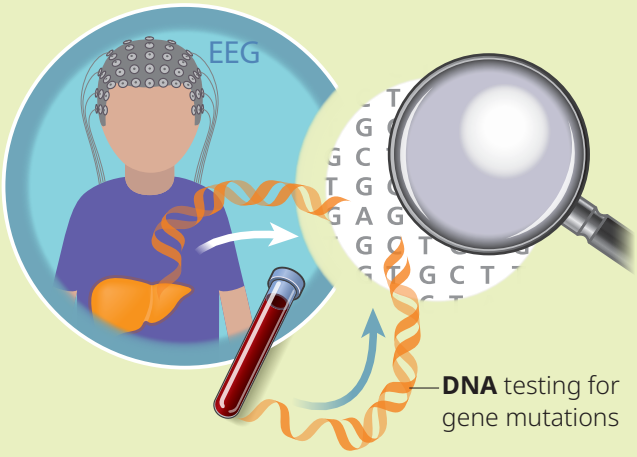
Risk of MISmanagement

Use of valproate in unrecognized POLG disease can trigger fatal liver failure

Early diagnosis is critical for treatment planning and genetic counselling

Tests

- Genetic testing
- EEG
- Labs (esp. LFTs)
- Neuroimaging (e.g., MRI)
- Neurophysiological (EMG/NCV)



Clinical trials and research

Research is ongoing into:

- **Nucleoside bypass therapy** to restore mitochondrial DNA replication by supplementing key building blocks
- **POLG modulators** to enhance or stabilize polymerase gamma function
- **Mitochondrial membrane stabilizers**, to protect and support mitochondrial integrity under stress
- **Gene therapy** to correct the underlying genetic defect directly at its source (preclinical stage)

Resources

POLG Foundation: polgfoundation.org
United Mitochondrial Disease Foundation (UMDF): umdf.org
World Mitochondria Society: wms-site.com
MMN Research Group: bit.ly/MMN-University-Bergen
Mitochondrial Medicine Society: mitosoc.org
MitoAction: mitoaction.org
Rare Epilepsy Network (REN): rareepilepsynetwork.org

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