

# POLG-related disorders

## POLG sequence analysis

**Disorder:** Mitochondrial disorders affect 1 in 5000 individuals, and mutations in mitochondrial DNA polymerase gamma (*POLG*) are identified in approximately 25% of those patients. *POLG* is the only DNA polymerase involved in mitochondrial DNA replication and mutations in this gene cause progressive depletion of mtDNA or accumulation of errors in mtDNA, which lead to dysfunction of mitochondria. There are no consistent genotype-phenotype correlations, as the same mutations have been found in individuals with different phenotypes.

There are six major clinical disorders which can be caused by mutations in *POLG*:

### 1. Alpers-Huttenlocher Syndrome (AHS)

- Age of onset: early childhood; rare cases of adult onset
- Symptoms: progressive, severe encephalopathy, intractable epilepsy and liver failure

### 2. Childhood myocerebrohepatopathy spectrum (MCHS)

- Age of onset: infancy to three years
- Symptoms: developmental delay or dementia, lactic acidosis, myopathy and failure to thrive

### 3. Myoclonic epilepsy, myopathy and sensory ataxia (MEMSA)

- Age of onset: young adulthood
- Symptoms: epilepsy, myopathy and ataxia without ophthalmoplegia
- Includes the disorder formerly known as SCAE (spinocerebellar ataxia with epilepsy)

### 4. Ataxia neuropathy spectrum (ANS)

- Median age of onset: 17 years
- Symptoms: ataxia and neuropathy, but seizures and ophthalmoplegia can also be seen
- Includes MIRAS (mitochondrial recessive ataxia syndrome) and SANDO (sensory neuropathy dysarthria and ophthalmoplegia)

### 5. Autosomal recessive progressive external ophthalmoplegia (arPEO)

- Median age of onset: 40 years
- Symptoms: progressive weakness of extraocular eye muscles which results in ptosis and ophthalmoparesis; typically no systemic involvement

### 6. Autosomal dominant progressive external ophthalmoplegia (adPEO)

- Median age of onset: 46 years
- Symptoms: generalized myopathy, sensorineural hearing loss, axonal neuropathy, ataxia, depression, Parkinsonism, hypogonadism, and cataracts
- Also known as chronic progressive external ophthalmoplegia plus (CPEO+)

### 7. Drug induced liver failure, particularly with anti convulsant drugs

Mutations in *POLG* have also been associated with MNGIE-like syndrome, MELAS, Parkinson's disease and premature menopause.

Additional information and test requisitions are available at: [www.cchmc.org/molecular-genetics](http://www.cchmc.org/molecular-genetics)

## Shipping Instructions:

Please enclose **test requisition** with sample.

**All information must be completed before sample can be processed.**

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

## Ship to:

Cytogenetics and Molecular Genetics Laboratories  
3333 Burnet Avenue NRB 1042  
Cincinnati, OH 45229  
513-636-4474



Human Genetics

Molecular Genetics Laboratory

CLIA#: 36D0656333

Phone: (513) 636-4474

Fax: (513) 636-4373

Email: [moleculargenetics@cchmc.org](mailto:moleculargenetics@cchmc.org)

[www.cincinnatichildrens.org/molecular-genetics](http://www.cincinnatichildrens.org/molecular-genetics)

## Indications:

- Confirmation of diagnosis in a patient with physical manifestation of mitochondrial disorder or *POLG*-related disorders
- Presymptomatic diagnosis and/or carrier testing in a relative of a patient with proven *POLG* mutation
- Prior to initiation of valproate therapy in a patient with intractable seizures, particularly with a history of psychomotor regression
- Prenatal diagnosis of an at-risk fetus, after confirmation of biallelic mutations in the parents (by prior arrangement only)

## Specimen:

**Blood:** 3mL whole blood in purple top (EDTA) tube.

**Cytobrush (buccal sample):** 6 cytobrushes sent at ambient temperature. Please call for free cytobrush collection kit.

Label each item with patient's name, birth date, and date of collection.

**Testing Methodology:** Sanger sequencing following PCR amplification of the coding and exon/intron boundaries of the *POLG* gene.

## Test Sensitivity:

**Clinical Sensitivity:** Three pathogenic mutations, 1399 G>A (A467T), 2243 G>C (W748S), and 2542 G>A (G848S), account for approximately 70% of mutations in affected individuals. Sequencing detects approximately 95% of mutations in *POLG*, with missense mutations accounting for 90% of *POLG* mutations. Large intragenic deletions have rarely been reported.

**Analytical Sensitivity:** The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic events will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

**Turn-Around Time:** 28 days

## CPT Codes:

*POLG* full gene sequencing: 81406

Family specific mutation analysis: 81403

Please call 1-866-450-4198 for pricing, insurance preauthorization, or with any billing questions.

**Results:** Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

## References:

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