POLG-related disorders

Defects of the nuclear and mitochondrial genome interaction

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Mitochondria are ubiquitous and play a crucial role in many vital functions, including oxidative phosphorylation and generation of adenosine triphosphate (ATP), calcium homeostasis, and apoptosis. Mitochondrial dysfunction results in neurologic and non-neurologic disorders manifesting with a broad spectrum of clinical phenotypes. In 1988, Holt and colleagues[1] reported the first pathogenic mitochondrial DNA (mtDNA) mutation in mitochondrial myopathies. Since then, numerous mtDNA mutations have been identified as the cause of various disorders. Among the most prototypical of these mitochondrial disorders, linked to primary defects in the mitochondrial genome, are mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS); myoclonic epilepsy and ragged red fibers; and neuropathy, ataxia, and retinitis pigmentosa. More than a decade after the initial reports, Van Goethem and colleagues[2] discovered, in patients with progressive external ophthalmoplegia (PEO), mutations in the nuclear gene polymerase γ (*POLG*), which were associated with mtDNA deletions. It is now well-established that primary defects in some nuclear genes are a common cause of mitochondrial diseases and that *POLG* is one of those nuclear genes.[3,4]

POLG Mitochondria contain their own DNA that encodes for 22 tRNA, 2 rRNA, and 13 respiratory chain protein subunits of complexes I, III, IV, and V.[5] Human mtDNA is continuously replicated by DNA polymerase γ. The mtDNA polymerase γ, in combination with the mitochondrial DNA helicase Twinkle and the mitochondrial single-stranded binding protein, forms the core replication apparatus in the mitochondria (figure 1).[6] The mitochondrial DNA polymerase γ is believed to be the sole polymerase responsible for mtDNA replication and repair in the mitochondria of eukaryotic cells.[7] The holoenzyme is a heterotrimer consisting of a catalytic subunit and 2 smaller accessory subunits.[6] The catalytic subunit (POLG) is encoded by *POLG* and has both polymerase and proofreading exonuclease activity resulting in high fidelity. It possesses an amino-terminal 3′→5′ exonuclease domain and a carboxy-terminal polymerase catalytic domain separated by a linker domain (figure 2).[8] The linker domain has an accessory determinant subdomain which forms an interface with the accessory subunit and enhance enzyme processivity (processivity is the measure of the average number of nucleotides incorporated by the enzyme before it dissociates from the template DNA).[6] The accessory subunit, which is encoded by *POLG2*, is required for proper DNA binding to ensure high processivity of the holoenzyme, allowing synthesis of thousands of nucleotides without dissociation.[9,10] Mutations in *POLG* compromise the enzyme function resulting in secondary mtDNA defects, including depletion, deletions, and base pair substitution, which in turn give rise to cellular dysfunction and various clinical phenotypes that appear across the lifespan.[11,12]

CLINICAL PHENOTYPE **Alpers syndrome and Alpers-like encephalopathy.** Alpers syndrome is one of the most severe and early manifestations of *POLG* recessive mutations. It is defined by the classic triad of early onset psychomotor regression, intractable seizures, and liver failure. Infants usually appear

GLOSSARY

ad = autosomal dominant; **ANT1** = adenine nucleotide translocator; **ar** = autosomal recessive; **ATP** = adenosine triphosphate; **COX** = cytochrome *c* oxidase; **MELAS** = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; **MNGIE** = mitochondrial neurogastrointestinal encephalomyopathy; **mtDNA** = mitochondrial DNA; **mtSSB** = mitochondrial single stranded binding protein; **PEO** = progressive external ophthalmoplegia; **POLG** = mitochondrial DNA polymerase γ-catalytic subunit; ***POLG*** = polymerase γ gene-catalytic subunit; ***POLG2*** = polymerase γ gene-accessory subunit; **RHADS** = rhythmic high-amplitude delta with superimposed spikes and polyspikes.

CME

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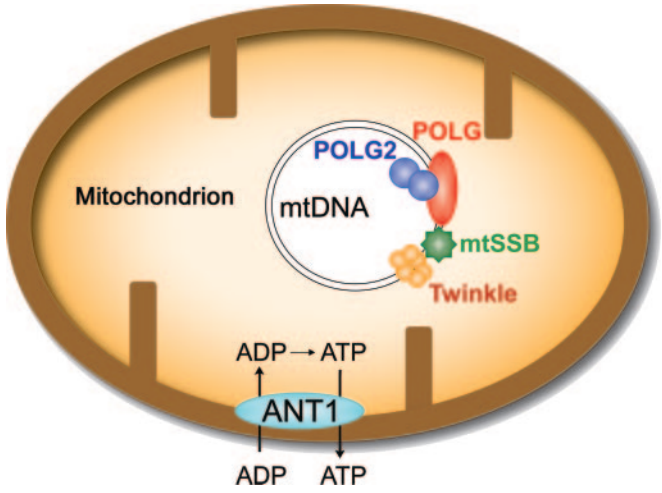
Study funding: Supported in part by the Mayo Clinic CTSA through grant UL1 RR024150 from NIH/NCRR.
Disclosure: Author disclosures are provided at the end of the article.

Figure 1 Schematic representation of the mitochondrion



Mitochondrial DNA (mtDNA) is replicated by the DNA polymerase γ with its catalytic subunit (POLG) and accessory subunits (POLG2). Twinkle unwinds the double-stranded DNA and creates the single-stranded DNA which is used to synthesize the complementary DNA strand. The DNA polymerase γ, Twinkle, and the mitochondrial single-stranded binding protein (mtSSB) form the core replication apparatus of the mtDNA. One of the major functions of the mitochondria is the generation of adenosine triphosphate (ATP). This is transported from the matrix to the cytosol by the adenine nucleotide translocator (ANT1) which also transports cytosolic ADP into mitochondria. POLG, POLG2, Twinkle, and ANT1 are nuclear-encoded proteins.

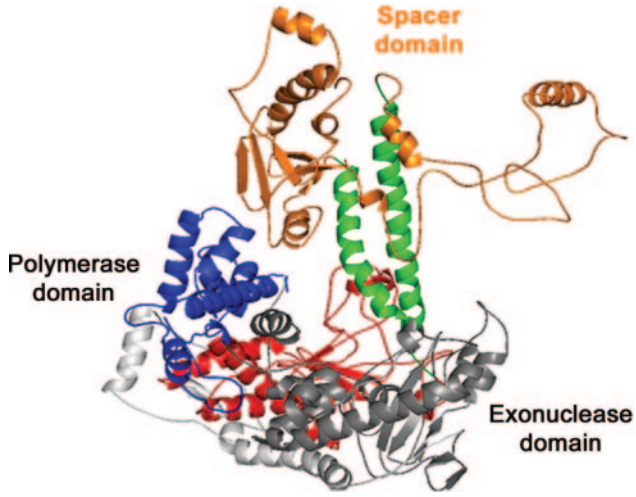
healthy at birth and may develop normally until the onset of the disease in infancy, although some infants may have a congenital static encephalopathy prior to the progression.[13] Seizures can be partial with or without secondary generalization, myoclonic or primary generalized. Epilepsia partialis continua and cortical blindness are common. Liver dysfunction often precedes the onset of the neurologic symptoms but it can also be precipitated by environmental factors such as infections or treatment with valproate. Refractory status epilepticus, which can be the first manifestation of the disease,[14] and liver failure are common causes of death, often occurring before the age of 3 years.[15]

Childhood and juvenile-onset Alpers syndrome and Alpers-like encephalopathy without liver failure are clinical variants of the more classic Alpers syndrome.[16–18] Other clinical manifestations include renal tubular acidosis, pancreatitis, cyclic vomiting, and hearing loss.[19]

Progressive occipital and thalamic MRI lesions, including increased cortical signal intensity on diffusion-weighted MRI, are often observed in both early-onset and juvenile Alpers.[18,20,21] Increased signal intensity in the cerebellum is also common. The MRI abnormalities can be detected prenatally and can be rapidly progressive,[18,22,23] but the MRI can also be normal (figure 3A). Gray matter neuronal loss with reactive astrocytosis is the pathologic correlate in Alpers syndrome.[15]

The correlation of clinical features with mutations is not uniform. Screening for *POLG* mutations in children with Alpers syndrome–like neuropathologic changes but no liver involvement did not reveal POLG mutations, suggesting that the pathologic changes are not *POLG*-specific.[24]

Figure 2 Schematic structure and function of POLG



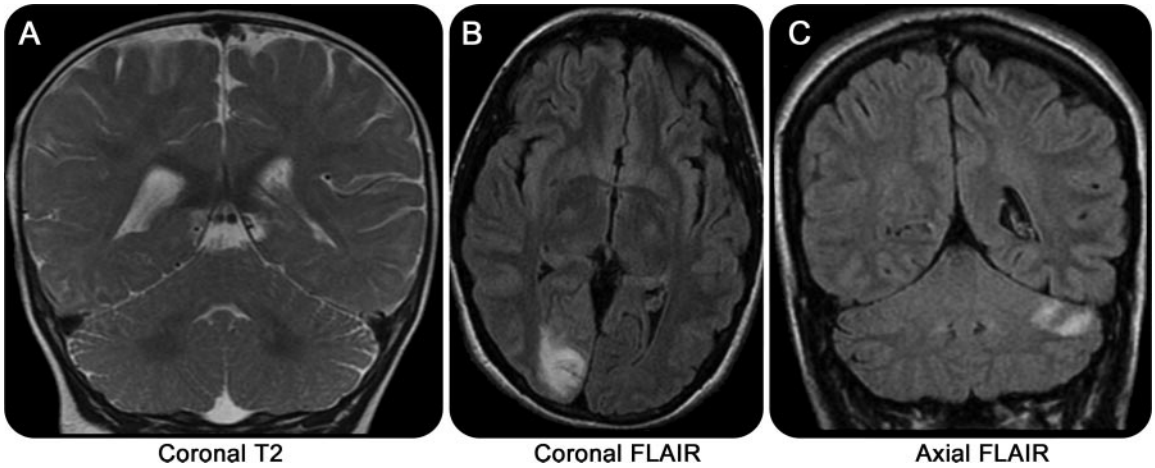
The polymerase and the exonuclease domains are connected by a large spacer domain (reprinted from Lee et al.,[6] copyright © 2009, with permission from Elsevier). POLG = mitochondrial DNA polymerase γ-catalytic subunit.

Ataxia neuropathy spectrum and epilepsy. Sensory or cerebellar ataxia can be a manifestation of recessive *POLG* mutations. The neuropathy is predominantly axonal and manifests as sensorimotor peripheral neuropathy, sensory neuropathy, or sensory ganglionopathy. Peripheral neuropathy with demyelinating features has also been described.[25,26] Involvement of the central proprioceptive pathways can contribute to the ataxia.[27] PEO, myopathy, dysarthria, myoclonus, epilepsy, and other clinical manifestations in different combinations can accompany the ataxia, leading to different phenotypes, such as myoclonic epilepsy myopathy sensory ataxia, sensory ataxia neuropathy dysarthria and ophthalmoplegia, and spinocerebellar ataxia with epilepsy.[28] Often, however, the phenotypes overlap and it may be difficult to fit patients into a specific phenotype.

POLG seems a leading gene for cerebellar ataxia in Central Europe, when the ataxia manifests under age 25 years; it is associated with PEO or sensory neuropathy.[29] *POLG* mutations have also been identified in a patient with multiple system atrophy of cerebellar subtype,[30] but additional studies are needed to establish if this represents an isolated case or if POLG plays a role in the etiology of multiple system atrophy.

Although epilepsy is a key feature of Alpers syndrome, it can accompany other phenotypes. The sei-

Figure 3 Brain MRI from patients with POLG-related disorders



(A) Normal coronal T2 image of a 10-month-old infant with Alpers syndrome. (B) Axial fluid-attenuated inversion recovery (FLAIR) of a 15-year-old girl with myopathy, cognitive decline, epilepsy, and ataxia reveals a left occipital infarct. (C) Coronal FLAIR of a 19-year-old woman with pharmacologically resistant epilepsy and stroke-like events shows a left cerebellar infarct. POLG = mitochondrial DNA polymerase γ-catalytic subunit.

zure semeiology includes simple and complex partial seizures, clonic and myoclonic seizures with epilepsia partialis continua, and convulsive status epilepticus.[20] Positive and negative visual phenomena are common manifestations of seizures. The seizures often result in radiologic abnormalities with stroke-like appearance, mimicking MELAS. Convulsive status epilepticus carries a poor prognosis with high risk of mortality.[20,31] There is no standardized antiepileptic regimen to treat the seizures, which are often refractory, but valproate is contraindicated because of the high risk of liver failure in these patients.[16,31–34] A combination of several antiepileptic drugs, including IV magnesium, is often required to abort the status epilepticus.[20,35]

Imaging findings are variable. MRI abnormalities include generalized cerebral atrophy, selective cerebellar atrophy, and multifocal T2 signal abnormalities with occipital lobe predilection (figure 3B).

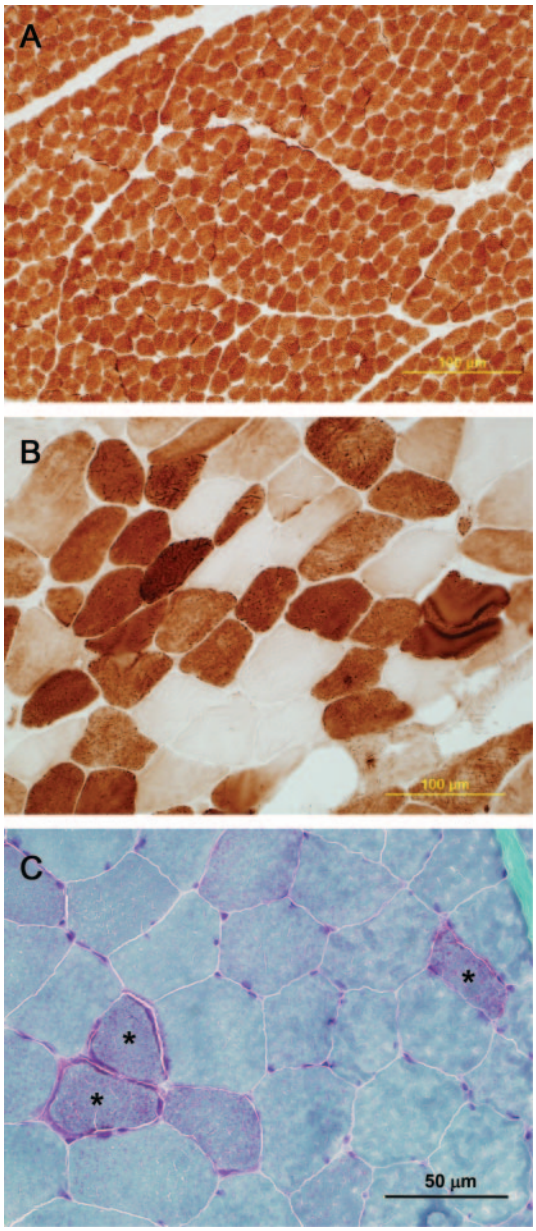
PEO and others. Autosomal dominant (ad) and autosomal recessive (ar) *POLG* mutations can result in PEO, which can occur as sole clinical manifestation of the disease or in association with limb myopathy. Parkinsonism, ovarian failure, and peripheral neuropathy can also accompany the ophthalmoparesis, the core clinical feature. While ovarian failure cosegregates with adPEO,[36,37] parkinsonism can accompany either adPEO or arPEO and is responsive to carbidopa.[36,38]

Less common clinical manifestations include early-onset dyschromatopsia and optic atrophy preceding the PEO and myopathy, mimicking OPA1-related disorders.[38] CSF oligoclonal bands can accompany the visual loss, mimicking multiple sclerosis.[14] Psychiatric symptoms, dementia,[28] cardiac arrhythmia and cardiomyopathy, palatal tremor,[27,39] hearing loss, stroke-like (figure 3C), diabetes, and gastrointestinal dysmotility may complicate the clinical picture. The latter can be so prominent that the patient may have a mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)–like phenotype, but the lack of extensive leukoencephalopathy and normal thymidine and deoxyuridine level in plasma would argue against thymidine phosphorylase deficiency.[40,41]

Rare patients have presented with isolate distal myopathy of the upper extremities[42] and fatal congenital myopathy.[43]

LABORATORY DATA **Muscle histology and respiratory chain enzyme activity.** Muscle histochemical studies may reveal normal findings or signs of mitochondrial dysfunction, varying from the combination of ragged-red, ragged-blue, and cytochrome *c* oxidase (COX)–negative fibers to isolated scattered COX-negative fibers. The histologic findings do not correlate with the severity of the phenotype or the patient's age (figure 4). Normal histologic findings can be observed in children with Alpers syndrome[24] or in adults with various phenotypes.[25,27] Similarly, biochemical assay of respiratory chain enzyme complexes may reveal decreased activity in single or multiple complexes, or normal activity, not only in adults, but also in children with Alpers syndrome.[24,27,44] Therefore, the clinical suspicion of a POLG-related disorder should lead to *POLG* analysis, despite the lack of histologic signs of mitochondrial dysfunction and the normal respiratory chain enzyme assay.

Figure 4 Muscle biopsy findings in patients with POLG-related disorders



(A) Cytochrome c oxidase staining reveals no COX(−) fibers in a 10-month-old infant with Alpers syndrome and (B) numerous COX(−) fibers (unstained fibers) in a 34-year-old woman with progressive external ophthalmoplegia, myopathy, and ataxia. (C) Trichrome staining showed scattered ragged-red fibers (asterisk) in a 19-year-old woman with epilepsy, ataxia, and stroke-like events. POLG = mitochondrial DNA polymerase γ-catalytic subunit.

Analysis of changes in mitochondrial DNA. Marked mtDNA depletion (reduction of the mtDNA copy number) in liver usually occurs in the setting of severe early-onset disease, such as Alpers and Alpers-like syndrome, while adult patients with PEO or later-onset disease and milder phenotype often show multiple mtDNA deletions without depletion in muscle.[12,27,45] However, mtDNA depletion or the combination of mtDNA deletions and depletion has been detected in patients with milder phenotypes, such as PEO or distal myopathy.[42,46] Conversely, children with Alpers and Alpers-like syndrome may lack mtDNA depletion.[24] Analysis of mtDNA copy number in blood samples is usually not informative.[45,47]

Table Features of the POLG disease-associated mutations

	Class I	Class II	Class III
Location	Polymerase catalytic domain	Putative DNA-binding channel	Interface POLG-POLG2
Effect	Reduced enzyme catalytic activity	Reduced DNA binding activity	Reduced processivity

Abbreviations: POLG = mitochondrial DNA polymerase γ-catalytic subunit; POLG2 = mitochondrial DNA polymerase γ-accessory subunit.

EEG An occipital EEG focus is frequently present in patients with seizures even in the absence of MRI changes in the occipital lobes.[31] Focal occipital predilection has been observed also in multifocal epilepsy.[20] In Alpers syndrome, rhythmic high-amplitude δ with superimposed spikes and polyspikes (RHADS) may be associated with the initial acute phase of the disease and distinctive of it.[21]

MUTATIONAL ANALYSIS A number of mutations have been identified across the entire *POLG* gene. These include missense, nonsense, splice-site mutations, deletions, and insertions with no hot spots (http://tools.niehs.nih.gov/polg/). Missense mutations account for more than 90% of all *POLG* mutations, while intragenic large deletions are rare.[11,12,48] The p.A467T is the most common mutation, accounting for ~31% of all mutant alleles, and is associated with a broad clinical spectrum of the disease.[12] The p.L304R mutation appears to be from South Asian populations.[12]

On the basis of the crystal structure of the human POLG, disease-associated mutations have been divided in 3 classes (table).[6] Class I mutations cluster in the active site of the polymerase domain and result in reduced catalytic enzyme activity. Class II mutations are located in the putative DNA-binding channel and reduce the DNA binding affinity. Class III mutations lie at the interface between POLG and POLG2, thus disrupting their interaction and reducing enzyme processivity. The different locations and function of the various mutations do not dictate the phenotype; no consistent correlation has emerged between genotype and phenotype. Phenotypic variability within the same family can also occur.[27,49]

DIAGNOSIS Due to the clinical heterogeneity, the overlapping phenotypes, the still-evolving spectrum

of these disorders, and the inconsistent muscle histologic and biochemical findings, the definitive diagnosis of POLG-related disorders relies on the identification of deleterious *POLG* mutations.

TREATMENT There is no effective treatment for POLG-related disorders and the care remains supportive.

DISCLOSURE

Dr. Milone receives research support from the Mayo Clinic CTSA through grant UL1 RR024150 from NIH/NCRR. Dr. Benarroch and Dr. Wong report no disclosures.

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Neurology 2011;77;1847-1852
DOI 10.1212/WNL.0b013e318238863a