POLG gene

DNA polymerase gamma, catalytic subunit

Normal Function

The *POLG* gene provides instructions for making the active piece, called the alpha subunit, of a protein called polymerase gamma (pol γ). To be most effective, the alpha subunit attaches to two copies of another protein called the beta subunit to form pol γ. Pol γ is a DNA polymerase, which is a type of enzyme that "reads" sequences of DNA and uses them as templates to produce new DNA. These enzymes are important for copying (replicating) cells' genetic material. DNA polymerases also play critical roles in DNA repair.

Pol γ functions in mitochondria. Mitochondria are structures within cells in which a process called oxidative phosphorylation converts the energy from food into a form that cells can use. Mitochondria each contain a small amount of DNA, known as mitochondrial DNA (mtDNA), which is essential for the normal function of these structures. Pol γ is the only DNA polymerase that is active in mitochondria and that can replicate mtDNA.

Health Conditions Related to Genetic Changes

Alpers-Huttenlocher syndrome

There are many variants (also called mutations) in the *POLG* gene that cause Alpers-Huttenlocher syndrome. Alpers-Huttenlocher syndrome is part of a group of conditions called *POLG*-related disorders that have overlapping signs and symptoms affecting muscle-, nerve-, and brain-related functions. Alpers-Huttenlocher syndrome is characterized by seizures, loss of mental and movement abilities (psychomotor regression), and liver disease. The liver disease in Alpers-Huttenlocher syndrome can be brought on or made worse by valproic acid, a common treatment for seizures.

Most *POLG* gene variants change single protein building blocks (amino acids) in the alpha subunit of pol γ. The variants can have several effects on the function of pol γ. The alpha subunit may lose the ability to attach to the beta subunits to form pol γ. Alternately, altered pol γ may be unable to bind the existing mtDNA strand to use as a template. Or, it may have a reduced ability to attract the DNA building blocks (nucleotides) that it uses to form new DNA. These effects impair DNA synthesis and may lead to insertion of the wrong nucleotide and decreased ability to fix the error.

The most common *POLG* gene variant in Alpers-Huttenlocher syndrome replaces the amino acid alanine with the amino acid threonine at position 467 (written as Ala467Thr or A467T). This variant blocks the ability of the alpha subunit to attach to the beta subunits and reduces pol γ's ability to synthesize DNA. The Ala467Thr variant is also common in other *POLG*-related disorders. The different conditions may be determined, in part, by the variant in the other copy of *POLG*, but there are still some variant combinations that can cause more than one of the disorders. It is unclear how the same variant can lead to different conditions.

Although the mechanism is unknown, many people with Alpers-Huttenlocher syndrome have fewer copies of mtDNA (mtDNA depletion). This abnormality is seen only in the tissues affected by the disease. MtDNA depletion leads to impaired oxidative phosphorylation and a decrease in cellular energy. These impairments affect tissues whose cells do not divide continually, such as brain, muscle, and liver. These tissues are most affected because they are more dependent on oxidative phosphorylation for energy, and impaired cells in these tissues are not generally replaced by new cells. The lack of energy supplies in these tissues could account for the signs and symptoms of Alpers-Huttenlocher syndrome.

Ataxia neuropathy spectrum

Another condition caused by variants in the *POLG* gene is ataxia neuropathy spectrum, a *POLG*-related disorder that is characterized by problems with coordination and balance (ataxia) and disturbances in nerve function (neuropathy). The conditions previously named mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) are now included in the ataxia neuropathy spectrum.

As mentioned above, most variants in the *POLG* gene change single amino acids in the alpha subunit of pol γ, and these variants can have several effects on the function of pol γ . As a result, pol γ has a reduced ability to replicate mtDNA. The most common *POLG* gene variant in ataxia neuropathy spectrum is the same as that in Alpers-Huttenlocher syndrome (described above), Ala467Thr. It is unclear how the same variant can lead to different disorders.

As in other *POLG*-related disorders, people with ataxia neuropathy spectrum typically have mtDNA depletion in the tissues affected by the condition, such as the brain. MtDNA depletion decreases the amount of energy available to the cell due to reduced oxidative phosphorylation, which may account for the signs and symptoms of ataxia neuropathy spectrum.

Childhood myocerebrohepatopathy spectrum

Childhood myocerebrohepatopathy syndrome (MCHS) is also caused by variants in the *POLG* gene. MCHS is a *POLG*-related disorder that affects the muscles (myo-), brain (cerebro-), and liver (hepato-).

Many variants in the *POLG* gene can cause MCHS. Most of these variants change

single amino acids in the alpha subunit of pol γ. These variants reduce the activity of pol γ, decreasing mtDNA replication.

As in other *POLG*-related disorders, people with MCHS typically have mtDNA depletion in muscle, brain, or liver tissue. MtDNA depletion impairs oxidative phosphorylation in these tissues and decreases the energy available to the cells, which may cause the signs and symptoms of MCHS.

Mitochondrial neurogastrointestinal encephalopathy disease

MedlinePlus Genetics provides information about Mitochondrial neurogastrointestinal encephalopathy disease

Myoclonic epilepsy myopathy sensory ataxia

Variants in the *POLG* gene cause another *POLG*-related disorder called myoclonic epilepsy myopathy sensory ataxia (MEMSA), which is characterized by recurrent seizures (epilepsy), muscle weakness (myopathy), and problems with coordination and balance (ataxia).

Most of the *POLG* gene variants involved in MEMSA change single amino acids in the alpha subunit of pol γ. These variants result in a less active form of pol γ that has a reduced ability to replicate mtDNA.

As in other *POLG*-related disorders, people with MEMSA typically have mtDNA depletion in affected tissues, such as muscle or brain. MtDNA depletion leads to impaired oxidative phosphorylation and decreased energy reserves in affected tissues, which may cause the signs and symptoms of MEMSA.

Progressive external ophthalmoplegia

Variants in the *POLG* gene are frequently responsible for an eye condition called progressive external ophthalmoplegia, another *POLG*-related disorder. This condition weakens the muscles that control eye movement and causes the eyelids to droop (ptosis).

There are at least 67 *POLG* gene variants that cause progressive external ophthalmoplegia. Most *POLG* gene variants change single amino acids in the alpha subunit of pol γ, which decreases the efficiency of mtDNA replication. As in another *POLG*-related disorder, Alpers-Huttenlocher syndrome (described above), the most common *POLG* gene variant in progressive external ophthalmoplegia is Ala467Thr. It is unclear how the same variants can lead to different disorders.

In progressive external ophthalmoplegia, variants in the *POLG* gene result in large deletions of genetic material from mtDNA in muscle tissue, rather than the overall mtDNA depletion seen in other *POLG*-related disorders. The reason for this difference is unknown. Researchers have not determined how deletions of mtDNA lead to the specific signs and symptoms of progressive external ophthalmoplegia, although the features of the condition are probably related to impaired oxidative phosphorylation. It

has been suggested that eye muscles are commonly affected by mitochondrial defects because they are especially dependent on oxidative phosphorylation for energy.

Leigh syndrome

MedlinePlus Genetics provides information about Leigh syndrome

Other Names for This Gene

- DNA polymerase subunit gamma-1
- mitochondrial DNA polymerase catalytic subunit
- PolG, catalytic subunit
- PolG-alpha
- POLG1
- POLGA
- polymerase (DNA directed), gamma
- polymerase (DNA) gamma, catalytic subunit

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of POLG (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5428[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28POLG%5BTIAB%5D%29+OR+%28polymerase+gamma%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- POLYMERASE, DNA, GAMMA; POLG (https://omim.org/entry/174763)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5428)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=POLG[gene])

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Genomic Location

The *POLG* gene is found on chromosome 15 (https://medlineplus.gov/genetics/chromosome/15/).

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