GeneDx
DNA Diagnostic Services

Test Information Sheet

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POLG Gene Sequence Analysis for Mitochondrial Disorders

Mendelian Inheritance in Man Numbers:

157640 Progressive external ophthalmoplegia (autosomal dominant) (PEPA1)
258450 Progressive external ophthalmoplegia (autosomal recessive) (PEOB1)
607459 Sensory ataxic neuropathy dysarthria and opthalmoparesis (SANDO)
203700 Alpers syndrome (Alpers-Huttenlocher syndrome)
603041 Mitochondrial nasogastrointestinal exencephalopathy syndrome (MNGIE)
174763 *POLG* gene

***Clinical features*:**

POLG gene mutations are one of the most common causes of inherited mitochondrial disease. Mutations in the *POLG* gene cause a spectrum of mitochondrial diseases (see above), with onset ages from the neonatal period to late adult life, including PEO, SANDO, Alpers syndrome, and MNGIE. The clinical presentation ranges from severe encephalopathy and liver failure to late onset external ophthalmoplegia, seizures, ataxia, myopathy and isolated muscle pain. Other findings include cardiomyopathy, cardiac conduction defects, depression, hearing loss, diffuse degeneration of cerebral gray matter, hepatic cirrhosis, and diffuse leukoencephalopathy. Parkinsonism and premature ovarian failure have also been described.[1] Because of the overlap in phenotypes and differences in age of onset, definitive diagnosis of these disorders is dependent upon mutation identification.

***Inheritance pattern*:** Autosomal recessive and autosomal dominant inheritance

Genetics and biochemical features:

MtDNA is replicated by DNA polymerase gamma (polγ), which is comprised of a 140 kD catalytic subunit and a 55 kD accessory subunit. *POLG* encodes the catalytic subunit of polγ. *POLG* mutations result in defects in the maintenance of the mitochondrial genome that results in dysfunction of the respiratory chain. Patients may have decreased cytochrome C oxidase (COX) activity along with mtDNA deletions or mtDNA depletion in symptomatic tissues. The *POLG* gene is located on chromosome 15q25 and has 22 coding exons.

***Reasons for referral*:**

1. Confirmation of biochemical and clinical diagnosis
2. Carrier testing
3. Genetic counseling
4. Prenatal diagnosis when familial mutations are known

***Test method*:**

Mutation analysis of the *POLG* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test sensitivity:

In two large studies sequence analysis was performed to identify mutations in the *POLG* gene in 350 and 232 patients exhibiting a *POLG*-related phenotype.[2,3] Between 8%-9% of the patients had an autosomal recessive *POLG*-related phenotype and had two known *POLG* mutations .[2,3] Several patients with a known autosomal dominant *POLG*-related phenotype had a single *POLG* mutation identified. In addition, approximately 4-7% of patients had a single *POLG* mutation identified but could not be classified as having an autosomal dominant or autosomal recessive POLG-related phenotype.[2,3] A separate report of 27 individuals with sporadic CPEO, found a *POLG* mutation in 7 (~26%) with two *POLG* mutations identified in 3 individuals and a single *POLG* mutation identified in the remaining 4.[4] Recent evidence showed that certain mutations in the *POLG* gene can lead to a range

of clinical phenotypes which predispose to development of liver failure after exposure to valproic acid. [1,5]

Mutation spectrum:

POLG mutations occur along the entire coding region of the gene. Genotype-phenotype correlations have been reported with severe mutations in the linker region or polymerase domain being reported in association with severe disease in children, however severe mutations have been reported elsewhere in the gene and adult onset mutations have been found in these regions as well. To date, 115 mutations including 91 missense, 8 nonsense, 4 splicing, 2 small deletion, 6 small insertions, 1 small insertion/deletion and 1 gross deletion have been reported in the HGMD database.

Specimen Requirements and Shipping/Handling:

- *Blood*: A single tube with 5 mL whole blood in EDTA (2mL for infants). Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for one week prior to shipping.
- *Buccal Brushes*: **Buccal brushes are not accepted for children under 6 months of age.** For adults and children over 6 months, a GeneDx buccal kit (others not accepted) can be used as an alternative to blood. Submit by mail.
- *Prenatal Diagnosis:* 10 mL amniotic fluid, 5 mg CVS, or 2 T25 flasks. Ship overnight at ambient temperature, using a cool pack in hot weather. Call to discuss requirements for parental blood. Keep backup cultures.

Required Forms:

Sample Submission (Requisition) Form – complete all pages
Payment Options Form or Institutional Billing Instructions

Prices and Turn-Around Time - *Fees are subject to change without notice:*

Test# 394 Mutation detection in a new patient	$ 2100	Approx. 6 weeks
Test# 9011 (9012) Testing of a relative for one (two) specific known mutations	$ 350 ($500)	Approx. 2-3 weeks
Test# 902 Prenatal diagnosis for a specific known mutation (including maternal cell contamination studies)	$ 2000	Approx. 2 weeks

CPT codes for mutation detection in a new patient - *All codes and units apply:*

POLG sequence analysis
83891 x 1 unit = $ 10
83898 x 46 units = $ 785
83894 x 23 units = $ 180
83904 x 46 units = $1025
83892 x 2 units = $ 40
83912 x 2 units = $ 60
Total = $2100

ICD9 code that might apply to new patients having this diagnostic test:

277.87 Disorder of mitochondrial metabolism

References: 1. Horvath et al., (2006) Brain 129:1674-1684. 2. Wong et al., (2008) Hum Mutat 29:E150-E172. 3. Blok et al., (2009, Jul 2) J Med Genet [Epub ahead of print]. 4. Agostino et al., (2003) Neurology 60:1354-1356. 5. McFarland et al., (2008) Arch Dis Child 93:151-153.