POLG Gene Sequence Analysis for Mitochondrial Disorders

Clinical Features:
POLG gene variants are one of the most common causes of inherited mitochondrial disease. Pathogenic variants in the *POLG* gene cause a spectrum of mitochondrial diseases, with onset ages from the neonatal period to late adult life, including chronic progressive external ophthalmoplegia (PEO), sensory ataxic neuropathy dysarthria and opthalmoparesis (SANDO), Alpers syndrome, mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE).[1-4] 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.[1,2] Because of the overlap in phenotypes and differences in age of onset, definitive diagnosis of these disorders is dependent upon variant identification. Certain variants in the *POLG* gene can lead to a range of clinical phenotypes which predispose to development of liver failure after exposure to valproic acid. [1-3,6]

Inheritance:
Autosomal dominant and autosomal recessive

Genetics:
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* variants 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.

Test Methods:
Variant 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. Variants 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 a large study of 2,697 patients exhibiting a *POLG*-related phenotype, sequence analysis of the *POLG* gene identified informative variants in 136 (5%).[7] Ninety-two of these patients had

an autosomal recessive *POLG*-related phenotype and had two known *POLG* variants, and three patients had an autosomal dominant *POLG*-related phenotype and had a single variant identified. In 41 of the 136 patients an autosomal recessive *POLG*-related disorder was suspected but only a single *POLG* variant was identified.[7] A separate report of 27 individuals with sporadic CPEO found a *POLG* variant in seven individuals (~26%), two *POLG* variants identified in three individuals and a single *POLG* variant identified in the four individuals.[5] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:

POLG variants occur along the entire coding region of the gene. Genotype-phenotype correlations have been reported with severe variants in the linker region or polymerase domain being reported in association with severe disease in children, however severe variants have been reported elsewhere in the gene and adult onset variants have been found in these regions as well. At this time more than 200 variants have been described according to the Human Gene Variant Database [8]. In one study, 81 patients suspected of having a *POLG*-related disorder were evaluated for large deletions of the *POLG* gene and only a single large deletion was identified.[7]

References:

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