Leber Hereditary Optic Neuropathy (LHON) Variant Panel

Variant List: G3376A, G3460A, G3635A, G3697A, G3733A, G3733C, G3890A, C4171A, G10197A, T10663C, G11778A, G13042A, G13051A, T13094C, G13513A, G14459A, C14482A, C14482G, T14484C, A14495G, C14568T

Clinical Features:

Leber hereditary optic neuropathy (LHON) is characterized by bilateral, painless subacute visual failure that develops in young adults with males being 4-5 times more likely than females to be affected.[1] Indviduals with LHON are usually asymptomatic until developing blurred vision in the central visual field in one eye.[1] Similar symptoms appear in the other eye approximately 2-3 months later.[1] In approximately 25% of cases, both eyes are affected at onset.[1] After onset, the optic discs become atrophic. Significant improvements in vision are rare and most patients become legally blind.[1] Cardiac arrhythmias, postural tremor, peripheral neuropathy, nonspecific myopathy, and movement disorders are reported to be more common in patients with LHON than in the general population.[1] A multiple sclerosis-like illness has also been reported, mostly in women.[1]

Genetics:

LHON is caused by variants in the mitochondrial DNA (mtDNA). Four variants (3460 G>A, 11778 G>A, 14459 G>A and 14484 T>C) account for approximately 95% of patients with LHON, while the other variants included in this panel are expected to be rare causes of LHON.[1, 2] Each mitochondrion has multiple copies of mtDNA and there are hundreds to thousands of mitochondria per cell, dependent on the cell type. Usually mtDNA variants affect only a fraction of the mtDNA; the coexistence of normal and mutant mtDNA is called heteroplasmy. Patients with LHON generally have more than 70% mutant mtDNA in leukocytes.[1] Variants causing LHON have reduced penetrance; approximately 50% of males and 90% of females harboring a variant are unaffected.[1] Variants in mtDNA arise *de novo* or are maternally inherited. In most cases, mtDNA point variants are inherited.

Test Methods:

Using genomic DNA, the entire mitochondrial genome is amplified by long-range PCR and sequenced for the detection of the variants on this panel using Next Generation sequencing that allows deep parallel sequencing of large numbers of mtDNA variants concurrently.[14] DNA sequences are assembled and compared to the published mitochondrial genome reference sequences for analysis. The presence of any variants is confirmed by conventional dideoxy sequence analysis or other methods.

Test Sensitivity:

Greater than 95% of patients with LHON are expected to have one of the varaints included in this panel.[1] Heteroplasmy as low as 1.5% is expected to be detected by this test.

References:

1. Yu-Wai-Man et al. (2009) J. Med. Genet. 46 (3):145-58 (PMID: 19001017)
2. Lott et al. (2013) Curr Protoc Bioinformatics 44 :1.23.1-26 (PMID: 25489354)