Leber Hereditary Optic Neuropathy (LHON) Variant Panel

Variant List:

MT-ND1: m.3376 G>A, m.3460 G>A, m.3635 G>A, m.3697 G>A, m.3733 G>A, m.3733 G>C, m.3890 G>A, m.4171 C>A; *MT-ND3*: m.10197 G>A; *MT-ND4L*: m.10663 T>C; *MT-ND4*: m.11778 G>A; *MT-ND5*: m.13042 G>A, m.13051 G>A, m.13094 T>C, m. 13513 G>A; *MT:ND6*: m.14459 G>A, m.14482 C>A, m.14482 C>G, m.14484 T>C, m.14495 A>G, m.14568 C>T

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] Individuals 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 (m.3460 G>A, m.11778 G>A, m.14459 G>A and m.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 from the submitted sample, the entire mitochondrial genome is amplified and sequenced using Next Generation Sequencing. DNA sequence is assembled and evaluated for the presence of the included variants in comparison with the revised Cambridge Reference Sequence (rCRS GeneBank number NC_012920). Alternative sequencing or other detection methods may be used to analyze or confirm mtDNA variants.

Test Sensitivity:

Greater than 95% of patients with LHON are expected to have one of the variants included in this panel.[1] Next-generation sequencing may not detect mtDNA point variants present at less than 2% heteroplasmy.

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)

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