Genetic Testing for Mitochondrial Disorders at GeneDx

Leber Hereditary Optic Neuropathy (LHON)

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. Individuals with LHON are usually asymptomatic until developing blurred vision in the central visual field in one eye. Similar symptoms appear in the other eye approximately 2-3 months later. In approximately 25% of cases, both eyes are affected at onset. After onset, the optic discs become atrophic. Significant improvements in vision are rare and most patients become legally blind. 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. A multiple sclerosis-like illness has also been reported, mostly in women.

Genetics:
LHON is caused by mutations in the mitochondrial DNA (mtDNA). Four mutations (3460 G>A, 11778 G>A, 14459 G>A and 14484 T>C) account for approximately 95% of patients with LHON. Each mitochondrion has multiple copies of mtDNA and there are hundreds to thousands of mitochondria per cell, dependent on the cell type. Usually mtDNA mutations 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. Mutations causing LHON have reduced penetrance; approximately 50% of males and 90% of females harboring a mutation are unaffected. Mutations in mtDNA arise de novo or are maternally inherited. In most cases, mtDNA point mutations are inherited.

Reasons for referral:
1. Molecular confirmation of a clinical diagnosis
2. Testing of patients suspected of having LHON
3. Genetic counseling

Methods:
The relevant portions of the mitochondrial genome are PCR-amplified for the detection of 4 common mutations associated with LHON (3460 G>A, 11778 G>A, 14459 G>A and 14484 T>C). Bi-directional sequence is obtained and compared to the published mitochondrial reference sequence. 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:
Greater than 95% of patients with LHON are expected to harbor one of the 4 mitochondrial DNA mutations included in this panel. The remaining 5% of patients are expected to have a mutation elsewhere in the mitochondrial genome.

Specimen Requirements and Shipping/Handling:
- BLOOD: Whole blood in EDTA; Adults: 8-10 ml; Children: 4-6 ml; Infants: 2-3 ml. Ship blood overnight at ambient temperature, using a cool pack in hot weather. Blood specimens may be refrigerated for up to 7 days prior to shipping.
- EXTRACTED DNA is discouraged. Please call first if sending extracted DNA
- Buccal Brushes: NOT accepted for this test.
- Cultured fibroblasts NOT accepted for this test

Required Forms:
- Sample Submission (Requisition) Form – complete all relevant pages
- Payment Options Form or Institutional Billing Instructions
### Prices and Turn-Around Times - Fees are subject to change without notice:

<table>
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<tr>
<th>Test#</th>
<th>Description</th>
<th>CPT Codes-All codes and units apply</th>
<th>Contract Price</th>
<th>Turn Around Time</th>
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<tr>
<td>445</td>
<td>Leber’s Hereditary Optic Neuropathy (LHON) mutations panel</td>
<td>81479</td>
<td>$655</td>
<td>Approx. 3-4 weeks</td>
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<td>452</td>
<td>Testing for single mtDNA mutation (16 common mtDNA mutations only) with heteroplasmy detection: as low as 1%</td>
<td>81479</td>
<td>$505</td>
<td>Approx. 2-3 weeks</td>
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*Prenatal testing is not available for mtDNA mutations or deletions*

#### Possible ICD9 Codes:
- 277.87 Disorder of mitochondrial metabolism
- 377.16 Hereditary optic atrophy

#### References: