OPA1 Gene Analysis in Optic Atrophy Type 1

Mendelian Inheritance in Man Numbers: 165500 – Optic Atrophy Type 1
605290 - OPA1

Clinical features:
Optic atrophy type 1 (OPA1) is characterized by bilateral and symmetric optic nerve pallor associated with vision loss and color blindness. The age of onset is usually between 4 and 6 years. The optic nerve pallor is temporal in approximately 50% of individuals and global in approximately the other half. The visual impairment is usually moderate, but may range from insignificant to severe legal blindness, and the visual field defect is typically centrocecal, central or paracentral while the peripheral field is usually normal. The color blindness is usually described as acquired blue-yellow. More severe phenotypes have also been described in ~10% of OPA1 mutation carriers and include sensorineural deafness, ptosis, ataxia and myopathy. Patients with OPA1 mutations and multiple mtDNA deletions have also been described. The disease presentation is variable even within members of the same family with reduced penetrance reported. The prevalence of OPA1 is estimated at 1 in 50,000 in most populations and as high as 1 in 10,000 in Denmark. OPA1 is caused by mutations in the OPA1 gene that encodes an inner mitochondrial membrane protein critical for mtDNA maintenance and oxidative phosphorylation. The OPA1 gene is located on chromosome 3q28-q29 and has 31 exons.

Leber’s Hereditary Optic Neuropathy (LHON) is another hereditary optic neuropathy that is caused by mutations in the mitochondrial genome. Genetic testing for LHON is offered at GeneDx (please see separate information sheet found under mitochondrial disorders).

Inheritance pattern: Autosomal dominant; semi-dominant inheritance has been reported.

Reasons for referral:
1. Confirmation of a clinical diagnosis
2. Carrier testing
3. Genetic counseling
4. Prenatal diagnosis in at risk pregnancies

Test method:
Using genomic DNA obtained from blood (2-5 mL in EDTA), the coding exons and corresponding intron/exon boundaries are sequenced using a novel solid-state sequencing-by-synthesis process that allows sequencing a large number of amplicons in parallel. For analysis, DNA sequence is assembled and compared to the published genomic reference sequences. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. The presence of any potentially disease-associated sequence variant(s) is confirmed by conventional dideoxy DNA sequence analysis or oligo-array comparative genome hybridization (ExonArrayDx), as appropriate.

Test sensitivity:
In a large study of 980 cases of suspected hereditary optic neuropathy, mutations in the OPA1 gene were identified in 30%, of which 52% were familial cases and 48% were apparently sporadic cases. Large deletions and duplications of the OPA1 gene that would not be detectable by sequence analysis have been identified in 19% (8 out of 42) of patients with autosomal dominant optic atrophy (ADOA) who were negative for ten primary LHON-causing mitochondrial DNA mutations and mutations in the OPA1 and OPA3 genes by sequence analysis. In another study, genomic deletions in the OPA1 gene were identified in 25% (10 out of 40) of unrelated Danish ADOA patients who were negative for OPA1 point mutations. Patients with OPA1 mutations and multiple mtDNA deletions have also been described. Of 21 patients with multiple mtDNA deletions who did not have mutations in
**POLG1, POLG2, SLC25A4 or PEO1** (other genes associated with multiple mtDNA deletions), approximately 14% harbored an **OPA1** mutation.5

**Mutation spectrum:**
There are over 200 mutations reported in the **OPA1** gene that are spread throughout the coding sequence of the gene that include missense, nonsense, splicing, small deletions/insertions and large deletions/insertions with missense, splicing and small deletion mutations being most commonly seen. Most mutations are located in the GTPase domain and in the 3’ end of the coding region.1 A founder mutation (c.2826delT) has been identified in the Danish population.1 The p.Arg445His mutation has been reported in two families with optic atrophy plus hearing loss but has also been reported in a patient with optic atrophy who did not have hearing loss.7 Genotype/phenotype correlations have not been established.1

**Specimen Requirements and Shipping/Handling:**
- **Blood:** A single tube with 1-5 mL whole blood in EDTA (1-2mL 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:** **CANNOT be accepted for this test.**
- **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# 530 Gene sequencing AND del/dup testing in a new patient $ 2700 Approx. 8 weeks
- Test# 901 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:**

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**TOTAL** $ 2700

**ICD9 codes that might apply to new patients having this diagnostic test:**
- Hereditary Optic Atrophy 377.16
- Optic Atrophy 377.1
- Sensorineural hearing loss 389.1
- Ataxia 781.3

**References:**