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Genetic testing for optic atrophy

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of the genetic test for optic atrophy (OA). OA is mostly inherited in an autosomal dominant manner, rarely in an autosomal recessive manner, with an overall prevalence of 3/100,000 live births. It is caused by mutations in the *OPA1*, *OPA3* and *TMEM126A* genes. Clinical diagnosis is based on clinical findings, ophthalmological examination, OCT, visual evoked potentials (VEPs) and electroretinography. The genetic test is useful for confirming diagnosis, differential diagnosis, couple risk assessment and access to clinical trials.

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Optic atrophy

(other synonyms: OA; synonyms for OPA1: OPTIC ATROPHY, JUVENILE, KJER-TYPE OPTIC ATROPHY, OPTIC ATROPHY, KJER TYPE, OAK , DOA; synonyms for OPA3: OPTIC ATROPHY AND CATARACT, AUTOSOMAL DOMINANT, ADOAC; synonyms for OPA7: OPTIC ATROPHY 7 WITH OR WITHOUT AUDITORY NEUROPATHY)(Retrieved from Orphanet, OMIM.org)

General information about the disease

Optic atrophy (OA) is a rare heterogeneous congenital disorder characterized by an insidious decrease in visual acuity 6/10 to 2/10 (usually between ages 4 and 6 years (1), although rapid decline has also been reported in adults), temporal optic disc pallor, blue-yellow dyschromatopsia, and centrocecal scotoma of variable density (2). OA may be observed in syndromic and nonsyndromic contexts which generally share similar ophthalmogical symptoms. However, syndromic OA patients experience full penetrance and usually more severe visual deficits (3-5). Although OPA loci are all primarily associated with optic atrophy, in some cases they can be differentiated by secondary symptoms: OPA1 may be associated with deafness (DOAD) and other symptoms such as sensorineural hearing loss, or myopathy and peripheral neuropathy (DOA-plus), which account for 20% of all *OPA1* mutations (6). OPA3 may be associated with cataract dyschromatopsia without systematic axis, tremor, extrapyramidal rigidity, pes cavus and absence of deep tendon reflexes (7); OPA7 may be associated with mild auditory alterations and hypertrophic cardiopathy (8).

The estimated prevalence of OA is 3/100,000 in most world populations, but can reach 1/10,000 in Denmark where a founder effect has been identified (6,9).

The diagnosis of OA is based on clinical findings, ophthalmological examination, OCT, absent or delayed visual evoked potentials (VEPs) and electroretinography. It is confirmed by detection of pathogenic gene variants.

Differential diagnosis should consider disorders that range from inflammatory, demyelinating, ischemic, glaucomatous, toxic and metabolic optic neuropathies to other

hereditary optic neuropathies such as Leber hereditary optic neuropathy (LHON), a disease caused by mutations of mitochondrial DNA, which is the major differential diagnosis for optic atrophy type 1 (OPA1) (1).

Three genes have been identified as causative of OA: *OPA1* (75% of all patients) (10) (OMIM gene: 605290; OMIM disease: 165500), *OPA3* (OMIM gene: 606580; OMIM disease: 165300) inherited in an autosomal dominant manner, and *TMEM126A* (OPA7) (OMIM gene: 612988; OMIM disease: 612989), inherited in an autosomal recessive manner. All encode mitochondrial proteins. DOA penetrance is around 70%, but can vary from 100% (9) to 43% (11) depending on family, pathogenic variant and study criteria (6,10).

Pathogenic variants may include small intragenic deletions/insertions, splice-site, missense and nonsense variations. Partial or whole gene deletions/duplications of *OPA1* gene are also commonly reported. In *OPA1*, 27% of the pathogenic variations are missense, 27% are splice variants, 23.5% lead to frame shift, 16.5% are nonsense and 6% are deletions or duplications (10).

Aims of the test

- To determine the gene defect responsible for the pathology
- To confirm clinical diagnosis of the disease
- To determine carrier status for the disease.

Test characteristics

Experts centers/Published guidelines

The test is listed in the Orphanet database and is offered by 25 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 9 accredited medical genetic laboratories in the US.

The guidelines for clinical use of the test are described in "Genetics home reference" (ghr.nlm.nih.gov) and "Gene reviews" (1).

Test strategy

A multi-gene NGS panel is used for the detection of nucleotide variations in coding exons and flanking introns in the *OPA1, OPA3* and *TMEM126A* genes. Potentially causative variants and regions with low coverage are Sanger-sequenced. MLPA is used for detection of duplications and deletions in *OPA1* gene. Sanger sequencing is also used for family segregation studies.

The test identifies variations in known causative genes in patients suspected to have OA. To perform molecular diagnosis, a single sample of biological material is normally sufficient. This may be 1 ml blood in a sterile tube with 0.5 ml K3EDTA or 1 ml saliva in a sterile tube with 0.5 ml ethanol 95%. Sampling rarely has to be repeated. Gene-disease associations and the interpretation of genetic variants are rapidly developing fields. It is therefore possible that the genes mentioned in this note may change as new scientific data is acquired. It is also possible that genetic variants today defined as of "unknown or uncertain significance" may acquire clinical importance.

Genetic test results

Positive

Identification of pathogenic variants in *OPA1, OPA3* or *TMEM126A* genes confirms the clinical diagnosis and is an indication for family studies.

A pathogenic variant is known to be causative for a given genetic disorder based on previous reports or predicted to be causative based on the loss of protein function or expected significant damage to protein or protein/protein interactions. In this way it is possible to obtain a molecular diagnosis in new/other subjects, establish the risk of recurrence in family members and plan preventive and/or therapeutic measures.

Inconclusive

Detection of a variant of unknown or uncertain significance: a new variation and/or without any evident pathogenic significance or with insufficient or significant conflicting evidence to indicate it is likely benign or likely pathogenic for a given genetic disorder. In these cases, it is advisable to extend testing to the patient's relatives in order to assess variant segregation and clarify its contribution. In some cases it could be necessary to perform further examinations/tests or to do a clinical reassessment of pathological signs.

Negative

The absence of variations in the genomic regions investigated does not exclude a clinical diagnosis but suggests the possibility of:

- sequence variations in gene regions not investigated by this test, such as regulatory regions (5' and 3' UTR) and deep intronic regions;
- variations in other genes not investigated by the present test;
- alterations that cannot be identified by sequencing, such as large rearrangements that cause loss (deletion) or gain (duplication) of extended gene fragments.

Unexpected

Unexpected results may come out from the test, for example information regarding consanguinity; absence of family correlation or the possibility of developing genetically based diseases.

Risk for progeny

In autosomal dominant transmission, the probability that a carrier transmits the disease variant to his/her children is 50% in any pregnancy, independently of the sex of the conceived.

Autosomal recessive transmission needs that both healthy carrier parents transmit their disease variant to his/her children. In this case, the probability of having an affected boy or girl is therefore 25%.

Limits of the test

The test is limited by current scientific knowledge regarding the genes and disease.

Analytical sensitivity (proportion of positive tests when the genotype is truly present) and analytical specificity (proportion of negative tests when the genotype is not present)

NGS: Analytical sensitivity: >99% (with a minimum coverage of 10X); Analytical specificity: 99.99%.

SANGER: Analytical sensitivity: >99.99%; Analytical specificity: 99.99%.

MLPA: Analytical sensitivity: >99.99%; Analytical specificity: 99.99%.

Clinical sensitivity (proportion of positive tests if the disease is present) and clinical specificity (proportion of negative tests if the disease is not present)

Clinical sensitivity: Variations of the *OPA1* gene are the most common genetic cause of dominant optical atrophy. More than 200 variations of *OPA1* are reported in the literature; they affect a percentage of patients ranging from 10 to 67% (11,12).

Clinical specificity: is estimated at approximately 99.99% [Author's laboratory data] (13).

Prescription appropriateness

The genetic test is appropriate when:

a) the patient meets the diagnostic criteria for the disease;

b) the genetic test has diagnostic sensitivity greater than or equal to other published tests.

Clinical utility

Clinical management	Utility
Confirmation of clinical diagnosis	yes
Differential diagnosis	yes
Access to clinical trial (14)	yes
Couple risk assessment	yes

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