The EuroBiotech Journal
TECHNICAL REPORT
EBTNA UTILITY GENE TEST

Genetic testing for color vision deficiency

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for color vision deficiency (CVD). Deuteranopia affects 1 in 12 males and is inherited in an X-linked recessive manner. It is associated with variations in the *OPN1LW* (OMIM gene: 300822; OMIM disease: 303900) and *OPN1MW* (OMIM gene: 300821; OMIM disease: 303800) genes. Tritanopia has a prevalence of 1 in 10 000, is inherited in an autosomal dominant manner, and is related to variations in the *OPN1SW* (OMIM gene: 613522; OMIM disease: 190900) gene. Blue cone monochromatism has a prevalence of 1 in 100 000, is inherited in an X-linked recessive manner and is related to mutations in the *OPN1LW* (OMIM gene: 300822; OMIM disease: 303700) and *OPN1MW* (OMIM gene: 300821; OMIM disease: 303700) genes. Clinical diagnosis is based on clinical findings, ophthalmogical examination, family history, electroretingraphy, color vision testing and dark adaptometry. The genetic test is useful for confirming diagnosis, and for differential diagnosis, couple risk assessment and access to clinical trials.

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Published online: 27 October 2017
doi:10.24190/ISSN2564-615X/2017/S1.10

Color vision deficiency

(other synonyms: color blindness, color vision defects, defective color vision, vision defect, color) (Retrieved from Genetics Home Reference)

General information about the disease

Color vision deficiency (CVD) is a group of rare congenital defects that affect the cone cells responsible for perception of colors. Protan (red), deutan (green) and tritan (blue) defects are characterized by the absence of L, M and S cones. Red-green color blindness (deuteranopia) is the most common form, followed by blue-yellow color blindness (tritanopia) (1,2).

Blue cone monochromatism (BCM) is another less common but severe form of color vision deficiency which may be associated with other symptoms such as photophobia, myopia and pendular nystagmus.

The prevalence of CVD is estimated to be 1 in 12 males for deuteranopia, 1 in 10.000 for tritanopia and 1 in 100.000 for BCM.

Diagnosis of CVD is based on clinical findings, ophthalmogical examination, family history, electroretinography, color vision and dark adaptometry. It is confirmed by detection of pathogenic variants in known causative genes.

Differential diagnosis should consider achromatopsia, Leber congenital amaurosis and other types of cone dystrophy.

CVD is related to causative mutations change the copy number or sequence of the long (L), middle (M), or short (S) wavelength sensitive cone opsin genes. Deuteranopia is inherited in an X-linked recessive manner and associated with variations in the *OPN1LW* (OMIM gene: 300822; OMIM disease: 303900) and *OPN1MW* (OMIM gene: 300821;

OMIM disease: 303800) genes. Tritanopia in inherited in an autosomal dominant manner and related to variations in the *OPN1SW* gene (OMIM gene: 613522; OMIM disease: 190900). BCM is inherited in an X-linked recessive manner related to mutations in the *OPN1LW* (OMIM gene: 300822; OMIM disease: 303700) and *OPN1MW* (OMIM gene: 300821; OMIM disease: 303700) genes.

Tritanopia generally has incomplete penetrance (3), BCM and deuteranopia have complete penetrance (4).

Pathogenic variants may contain small intragenic deletions/insertions, splice-site, missense and nonsense variants; gene rearrangements are usually found in the *OPN1LW/OPN1MW* gene cluster and locus control region (4-6).

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 11 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 8 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).

Test strategy

Sanger sequencing is used for the detection of nucleotide variations in coding exons and flanking introns in the *OPN1MW, OPN1LW* and *OPN1SW* genes. A quantitative method is used for detection of duplications and deletions. Sanger sequencing is also used for family segregation studies.

The test identifies variations in known causative genes in patients suspected to have CVD. 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 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 the *OPN1MW, OPN1LW* or *OPN1SW* genes confirms 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 X-linked transmission, affected males only transmit the disease variant to their daughters. The probability that a female carrier transmits the pathogenic variant to her offspring is 50% in any pregnancy independently of the sex of the conceived. Females who inherit the pathogenic variant will be carriers and usually unaffected. Males who inherit the pathogenic variant will be affected.

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.

Limits of the test

The test is limited by the current state of 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)

SANGER: Analytical sensitivity: >90%; Analytical specificity: >95% (4).

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: >90% for *OPN1LW/OPNMW* gene cluster (4).

Clinical specificity: >95% for *OPN1LW/OPNMW* gene cluster (4).

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 (7)	yes
Couple risk assessment	yes

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