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Genetic testing for choroideremia

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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 choroideremia (CHM). CHM is an inherited X-linked recessive disorder associated with variations in the *CHM* gene. The overall prevalence of CHM varies from 1 in 50 000 to 1 in 100 000. Clinical diagnosis is based on clinical findings, ophthalmological examination, visual field, fundus autofluorescence, optical coherence tomography and electroretinography. The genetic test is useful for confirming diagnosis and for differential diagnosis, couple risk assessment and access to clinical trials.

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Choroideremia

(other synonyms: choroidalsclerosis, progressive tapetochoroidal dystrophy, TCD, CHM) (retrieved from genedx.com, OMIM.org)

General information about the disease

Choroideremia (CHM) is a rare inherited condition characterized by progressive chorioretinal degeneration and loss of vision that mainly affects males. In affected males symptoms typically evolve from night blindness to progressive constriction of the visual field (tunnel vision) and slow loss of visual acuity (1). These vision problems are due to progressive atrophy of the specialized light-sensitive cells in the neuroretina, of the retinal pigment epithelium and choriocapillaris. Cystoid macular edema (62.5%) has also been reported (2). Individuals with this condition typically develop blindness, most commonly in late adulthood. Carrier females are mostly asymptomatic, but may develop symptoms of night blindness and visual field loss later in life; careful fundus examination shows chorioretinal degeneration (3). CHM is classically an isolated ocular finding, though it may rarely be part of a contiguous gene syndrome involving Xq21 (4-6).

The estimated prevalence of CHM varies from 1 in 50 000 to 1 in 100 000 (7,8).

The diagnosis of CHM is based on clinical findings, ophthalmological examination, visual field, electroretinography, fundus autofluorescence and optical coherence tomography (2). It is confirmed by detection of the pathogenic variant of the gene.

Differential diagnosis should consider other retinal dystrophies such as retinitis pigmentosa (especially X-linked forms), Usher syndrome, gyrate atrophy of the choroid and retina and Bietti crystalline retinal dystrophy.

CHM is inherited in an X-linked recessive manner and is associated with variations in the *CHM* gene (OMIM gene: 300390; OMIM disease: 303100).

Pathogenic variants may include deletions, insertions, duplications, translocations, nonsense, splice-site, frameshift and missense mutations. Full gene and partial deletions represent 25–50% of mutations, and a further 30% are nonsense mutations resulting in premature termination of the REP-1 protein (8,9).

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 8 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 12 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), "Gene reviews" (8) and "Clinical Utility Gene Card" (10).

Test strategy

Sanger sequencing is used for the detection of nucleotide variations in coding exons and flanking introns of *CHM* gene and for family segregation studies. MLPA is used for detection of duplications and deletions in the gene.

The test identifies variations in known causative genes in patients suspected to have CHM. 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 gene 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 *CHM* gene 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

The gene has X-linked recessive 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.

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)

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 in *CHM* gene are identified in more than 95% of cases (8, 11-13).

Clinical specificity: is estimated at approximately 99.99% [Author's laboratory data] (14).

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 (15)	yes
Couple risk assessment	yes

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