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Genetic testing for Mendelian myopia

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for Mendelian myopia (MM), a large and heterogeneous group of inherited refraction disorders. Variations in the *SLC39A5, SCO2* and *COL2A1* genes have an autosomal dominant transmission, whereas those in the *LRPAP1, P3H2, LRP2* and *SLITRK6* genes have autosomal recessive transmission. The prevalence of MM is currently unknown.

Clinical diagnosis is based on clinical findings, family history, ophthalmological examination and other tests depending on complications. The genetic test is useful for confirming diagnosis, and for differential diagnosis, couple risk assessment and access to clinical trials.

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Mendelian myopia

(other synonyms: genetic myopia)

General information about the disease

Mendelian myopia (MM) is a large heterogeneous group of inherited refraction defects involving poor vision of distant objects and clear vision of close objects. The various forms are distinguished by the magnitude of the defect:

- mild (up to 3 diopters);
- medium (from 3 to 6 diopters);
- high (over 6 diopters).

MM is also classified as:

- isolated familial
- syndromic

and as:

- juvenile-onset myopia which develops and progresses between the ages of 10 and 16 years;
- "pathological" high-grade myopia, usually with onset in the perinatal period, associated with severe eye disorders such as retinal detachment, macular degeneration, glaucoma and rapid refractive error myopic shifts before the age of 10-12 years (1, 2).

Myopia (all forms) is a major cause of visual impairment worldwide. Its global prevalence of 28.3% (about two billion affected people) is expected to increase in the next decades (3). Studies of myopia in children suggest a prevalence of 7.3% when neither parent is myopic, 26.2% when one parent has myopia, and 45% when both parents are affected by myopia (4). The prevalence of genetically determined myopia, however, is currently unknown.

Diagnosis of MM is based on clinical findings, family history, ophthalmological examination and other examinations depending on type of complication. It is confirmed

by identification of pathogenic variants in causative genes by molecular genetic testing.

Differential diagnosis should consider other forms of myopia unrelated to Mendelian inheritance.

Although the nature of the visual defect is multifactorial, several studies have shown involvement of single genes in the development of early onset high-grade myopia. Isolated familial myopia can be inherited in an autosomal dominant manner associated with variations in *SCO2* (OMIM gene: 604272; OMIM disease: 608908) and *SLC39A5* (OMIM gene: 608730; OMIM disease: 615946) genes, and as autosomal recessive trait associated with variations in *LRPAP1* (OMIM gene: 104225; OMIM disease: 615431) and *P3H2* (OMIM gene: 610341; OMIM disease: 614292) genes (5-8).

There are also syndromic forms of myopia related to Donnai Barrow syndrome, caused by variations in the *LRP2* gene (OMIM gene: 600073; OMIM gene: 222448) (9) or to deafness-and-myopia syndrome, caused by variations in the *SLITRK6* gene (OMIM gene: 609681; OMIM disease: 221200) (10), both with autosomal recessive transmission, and Stickler syndrome type I caused by variations in the *COL2A1* gene (OMIM gene: 120140; OMIM disease: 108300) (11), with autosomal dominant transmission.

Pathogenic variants may include small intragenic deletions/insertions, splice site, missense and nonsense variations. For *SCO2* and *COL2A1* genes, partial or whole gene deletions/duplications are also commonly reported.

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, for genes with recessive autosomal inheritance.

Test characteristics

Expert centers/ Published guidelines

The test is listed in the Orphanet database and is offered by more than 23 accredited medical genetic laboratories in the EU, and in the GTR database, offered by about 16 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

A multi-gene NGS panel is used for the detection of nucleotide variations in coding exons and flanking introns in the *COL2A1, LRPAP1, LRP2, P3H2, SCO2, SLC39A5* and *SLITRK6* genes. Potentially causative variants and regions with low coverage are Sanger-sequenced. MLPA is used for detection of duplications and deletions in the *COL2A1* gene. Sanger sequencing is also used for family segregation studies.

The tests identify variations in known causative genes in patients suspected to have MM. 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 *COL2A1, LRPAP1, LRP2, P3H2, SCO2, SLC39A5* and *SLITRK6* 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:

- alterations that cannot be identified by sequencing, such as large rearrangements that cause loss (deletion) or gain (duplication) of extended gene fragments;
- 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.

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: due to the limited number of cases described, no clinical sensitivity for isolated familial myopia is available in the literature. Likewise, few families with Donnai Barrow (12) or deafness-and-myopia syndromes (10) have been described. However, variations in the *COL2A1* gene are identified in about 80-90% of cases with Stickler syndrome type I (11).

Clinical specificity: can be estimated at approximately 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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