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Genetic testing for Sorsby's fundus dystrophy

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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 Sorsby's fundus dystrophy (SFD). SFD is caused by variations in the *TIMP3* gene. Prevalence is, currently unknown. SFD has autosomal dominant inheritance. Clinical diagnosis is based on clinical findings, color vision testing, optical coherence tomography, ophthalmological examination 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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Sorsby's fundus dystrophy

(Other synonyms: Sorsby's pseudoinflammatory fundus dystrophy, SFD, hemorrhagic fundus dystrophy, hemorrhagic macular dystrophy) (retrieved from OMIM.org)

General information about the disease

Sorsby's fundus dystrophy (SFD) is a rare inherited disease with onset in the second to fourth decade of life. It is characterized by progressive degeneration of the posterior pole, hemorrhages, edema, metamorphopsia, exudate with drusen-like pigment deposits (1,2), night blindness and color vision deficiency.

The prevalence of SFD is currently unknown since there have been few publications on this disease.

Diagnosis is based on clinical findings, ophthalmological examination, color vision testing, optical coherence tomography (showing hyperreflectivity of the retinal pigment epithelium and retinal atrophy) (3) and electroretinography. It is confirmed by detection of pathogenic variants in the gene.

Differential diagnosis should consider other macular dystrophies, pattern dystrophies, occult macular dystrophy, AVMD and BVMD in advanced stages.

SFD is an autosomal dominant disorder caused by variations in the *TIMP3* gene (OMIM gene: 188826; OMIM disease: 136900) (4).

Pathogenic variants may include sequence variations (missense, nonsense, small insertions and deletions). Partial or whole gene deletions/duplications are generally not found.

Aims of 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

Expert centers/ Published guidelines

The test is listed in the Orphanet database and is offered by 7 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 7 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 TIMP3 gene. Sanger sequencing is also used for family segregation studies. 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 the TIMP3 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.

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.

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.

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.

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%.

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: About 15 variations of TIMP3 gene are described in patients with SFD, all reported in isolated or family cases (5,6). Variations are often caused by the founder effect and that is why there is no prevalence data.

Clinical specificity: is estimated at approximately 99.99% [Author's laboratory data] (7).

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 (8)	yes
Couple risk assessment	yes

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