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Genetic testing for familial exudative vitreoretinopathy

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for familial exudative vitreoretinopathy (FEVR). There is insufficient data to determine the prevalence of FEVR. Variations in the *FZD4 (OMIM gene: 604579; OMIM disease: 133780), TSPAN12 (OMIM gene: 613138; OMIM disease: 613310)* and *ZNF408 (OMIM gene: 616454; OMIM disease: 616468)* genes have autosomal dominant inheritance, whereas variations in *LRP5 (OMIM gene: 603506; OMIM disease: 601813)* have autosomal dominant or recessive inheritance and variations in *NDP* (OMIM gene: 300658; OMIM disease: 305390) have X-linked inheritance. Clinical diagnosis is based on clinical findings, family history, ophthalmological examination, fundoscopy, slit-lamp examination and fluorescein angiography. The genetic test is useful for confirming diagnosis and for differential diagnosis, couple risk assessment and access to clinical trials.

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Familial exudative vitreoretinopathy

(other synonyms: Criswick-Schepens Syndrome, FEVR)

General information about the disease

Familial exudative vitreoretinopathy (FEVR) is a rare, clinically heterogeneous, progressive(1) inherited disorder characterized by abnormal or incomplete vessel growth in the peripheral retina associated with ischemia or hemorrhage. The disorder typically has early onset and clinical findings include peripheral vision flashes or floaters, strabismus, cataract, leukocoria and vision loss in later stages. Other less frequent findings include fibrovascular masses, neovascularization, retinal traction and retinoschisis (2,3).

The prevalence of FEVR is currently unknown.

Diagnosis of FEVR is based on clinical findings, family history, ophthalmological examination, fundoscopy, slit-lamp examination and fluorescein angiography. It is confirmed by detection of pathogenic variants in causative genes by molecular genetic testing.

Differential diagnosis should mainly consider retinopathy of prematurity, persistent fetal vasculature syndrome, Norrie disease, Coats disease and toxocariasis.

FEVR is mostly inherited in an autosomal dominant manner, and more rarely in an X-linked recessive or autosomal recessive manner.

Variations in the *FZD4* (OMIM gene: 604579; OMIM disease: 133780), *TSPAN12* (OMIM gene: 613138; OMIM disease: 613310) and *ZNF408* (OMIM gene: 616454; OMIM disease: 616468) genes have autosomal dominant inheritance. Variations in the *LRP5* (OMIM gene: 603506; OMIM disease: 601813) gene have autosomal dominant or recessive inheritance and variations in the *NDP* (OMIM gene: 300658; OMIM disease: 305390) gene have X-linked inheritance.

Penetrance is reported to be 100% (4) on the basis of fluorescein angiography and as low as 10% on the basis of reduced vision.

Pathogenic variants may include sequence variations (missense, nonsense, splicing, small insertions and deletions). Partial or whole gene deletions/duplications are also commonly reported.

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

Experts centers/Published guidelines

The test is listed in the Orphanet database and is offered by more than 8 accredited medical genetic laboratories in the EU, and in the GTR database, offered by about 13 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"(5).

Test strategy

A multi-gene NGS panel is used for the detection of nucleotide variations in coding exons and flanking introns in the *FZD4, LRP5, NDP, TSPAN12* and *ZNF408* genes. Potentially causative variants and regions low coverage are Sanger-sequenced. MLPA is used for detection of duplications and deletions in FZD4, NDP and TSPAN12 genes. Sanger-sequenced is also used for family segregation studies.

The tests identify variations in known causative genes in patients suspected to have FEVR. 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 *FZD4, LRP5, NDP, TSPAN12* or *ZNF408* 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%.

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

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 in known causative genes cover about 50% of cases of FEVR (6).

Clinical specificity: is estimated at about 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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