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Genetic testing for Best vitelliform macular 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 Best vitelliform macular dystrophy (BVMD). BVMD is mostly inherited in an autosomal dominant manner (autosomal recessive transmission is rare). The overall prevalence is currently unknown. BVMD is caused by mutations in the *BEST1* gene. Clinical diagnosis is based on clinical findings, ophthalmological examination, optical coherence tomography, electrooculography 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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Best vitelliform macular dystrophy

(other synonyms: Vitelliform macular dystrophy, early-onset; Vitelliform macular dystrophy, juvenile-onset; Best macular dystrophy, BMD; Macular degeneration, polymorphic vitelline; Best vitelliform macular dystrophy, multifocal; Best disease, Vitelliform macular dystrophy type 2, VMD2) (Retrieved from Orphanet, OMIM.org)

General information about the disease

Best vitelliform macular dystrophy (BVMD) is an inherited progressive macular dystrophy with typical childhood onset (1). No retinal symptoms or signs are usually present at birth and typically do not manifest until age 5-10 years. BVMD is characterized by different stages of progression from completely asymptomatic (stage 0-1) to severely decreased central visual acuity (20/200), dyschromatopsia and metamorphopsia (stage 5). Peripheral vision and dark adaptation are generally normal. Age of onset and severity of vision loss vary within and between families.

The estimated prevalence of BVMD is between 1/5,000 and 1/67,000 in northern Sweden and Denmark, respectively, (2) while worldwide prevalence is unknown (1).

Diagnosis of BVMD is based on clinical findings, ophthalmological examination, optical coherence tomography, fundus autofluorescence, electrooculography and electroretinography (which reveals reduced central amplitudes) (3,4). It is confirmed by detection of pathogenic variants in the only causative gene (*BEST1*) (5,6).

Differential diagnosis should consider adult vitelliform macular dystrophy (AVMD), age-related macular degeneration (AMD), Bull's eye maculopathy, autosomal recessive bestrophinopathy, autosomal dominant vitreoretinochoroidopathy and retinitis pigmentosa.

BVMD is mainly inherited in an autosomal dominant manner and *BEST1 (*VMD2*)* (OMIM gene: 607854; OMIM disease: 153700) is the principal gene associated with it, although autosomal recessive inheritance has also been reported (7).

Pathogenic variants may contain small intragenic deletions/insertions, splice-site, missense and nonsense variants; exon or whole-gene duplications/deletions are not usually found. BVMD generally has complete penetrance (1).

Aims of testing

- 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 123 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 "Clinical Utility Gene Card" (8) and "Gene reviews" (1).

Test strategy

Sanger sequencing is used for the detection of nucleotide variations in coding exons and flanking introns in the *BEST1* gene. Sanger sequencing is also used for family segregation studies.

The test identifies variations in known causative genes in patients suspected to have BVMD. 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 *BEST1* 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)

SANGER: Analytical sensitivity: >98%; Analytical specificity: >98% (8).

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 *BEST1* gene are identified in more than 96% of cases having a family history positive for BVMD and in 50-70% of cases with a negative family history (1).

Clinical specificity: is estimated at approximately 99.99% [Author's laboratory data] (9).

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 (10)	yes
Couple risk assessment	yes

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