The EuroBiotech Journal
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TECHNICAL REPORT
EBTNA UTILITY GENE TEST

Genetic testing for Bietti crystalline 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 Bietti crystalline dystrophy (BCD). The disease has autosomal recessive inheritance, a prevalence of 1 per 67 000, and is caused by mutations in the *CYP4V2* gene. Clinical diagnosis is based on clinical findings, ophthalmological examination, electroretinography and optical coherence tomography. The genetic test is useful for confirming diagnosis, and for differential diagnosis, couple risk assessment and access to clinical trials.

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Published online: 27 October 2017
doi:10.24190/ISSN2564-615X/2017/S1.06

Bietti crystalline dystrophy

(other synonyms: BCD, Bietti crystalline corneoretinal dystrophy, Bietti crystalline retinopathy, Bietti tapetoretinal degeneration with marginal corneal dystrophy) (Retrieved from Orphanet, OMIM.org)

General information about the disease

Bietti crystalline dystrophy (BCD) is a rare inherited progressive chorioretinal degenerative disorder with onset typically in the second to third decades of life (1). It is characterized by atrophy and degeneration of the retinal pigment epithelium, (2,3) crystalline deposits in the posterior retina and/or corneal limbus, sclerosis of choroidal vessels (4) leading to progressive night blindness, narrowing of the visual field and impaired color vision. Central acuity can be normal until late in the disease when it becomes severely impaired.

BCD has been considered a rare disease, however some reports have associated BCD findings with some forms of autosomal recessive retinitis pigmentosa and for this reason the prevalence is estimated to 1 per 67 000.

The diagnosis of BCD is based on clinical findings, ophthalmological examination, visual field examination, electrophysiological testing (electroretinography - ERG) and optical coherence tomography (OCT). The diagnosis is then confirmed by molecular genetic analysis of the responsible gene.

Differential diagnosis should first consider retinitis pigmentosa, with which BCD shares many clinical features. Other diseases to consider are those associated with crystalline deposits, such as primary hyperoxaluria types 1 and 2, cystinosis, Sjögren Larsson syndrome, drug toxicity (tamoxifen, methoxyflurane, canthaxanthin) and drug abuse.

BCD is inherited in an autosomal recessive manner and the only causative gene is *CYP4V2* (OMIM gene: 608614; OMIM disease: 210370).

Pathogenic variants may contain small intragenic deletions/insertions, splice-site, missense and nonsense variations. Only one whole gene deletion is reported. (6).

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 5 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) and "Gene reviews" (1).

Test strategy

Sanger sequencing is used for the detection of nucleotide variations in coding exons and flanking introns in the *CYP4V2* gene. Sanger sequencing is also used for family segregation studies.

The test identifies variations in known causative genes in patients suspected to have BCD. 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 *CYP4V2* 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

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: >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 *CYP4V2* associated with BCD are identified in more than 93% of cases (1).

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 (≥93% of positive tests) (1).

Clinical utility

Clinical management	Utility
Confirmation of clinical diagnosis	yes
Differential diagnosis	yes
Access to clinical trial (8)	yes
Couple risk assessment	yes

Acknowledgment

Lucia Ziccardi contribution as part of "Fondazione Bietti" was supported by the Ministry oh Health and "Fondazione Roma".

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