The EuroBiotech Journal
TECHNICAL REPORT
EBTNA UTILITY GENE TEST

Genetic testing for Doyne honeycomb retinal dystrophy

Andi Abeshi[1,2], Pamela Coppola[3], Tommaso Beccari[4], Munis Dundar[5], Lucia Ziccardi[6] and Matteo Bertelli[2,3]

Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for Doyne honeycomb retinal dystrophy (DHRD). The disease has an autosomal dominant inheritance and is caused by variations in the *EFEMP1* gene. There is insufficient data to establish the prevalence of DHRD. Clinical diagnosis is based on clinical findings, ophthalmological examination, electroretinography, fluorescein angiography and optical coherence tomography. The genetic test is useful for confirming diagnosis, and for differential diagnosis, couple risk assessment and access to clinical trials.

[1]MAGI Balkans, Tirana, Albania
[2]MAGI'S Lab, Rovereto, Italy
[3]MAGI Euregio, Bolzano, Italy
[4]Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy
[5]Department of Medical Genetics, Erciyes University Medical School, Kayseri, Turkey
[6]Neurophthalmology Unit, "G.B. Bietti" Foundation IRCCS, Rome, Italy

Corresponding author: M. Bertelli
E-mail: info@assomagi.org

Published online: 27 October 2017
doi:10.24190/ISSN2564-615X/2017/S1.14

Doyne honeycomb retinal dystrophy

(other synonyms: Doyne honeycomb degeneration of retina, DHRD, malattia leventinese, MLVT, familial dominant drusen) (retrieved from OMIM.org)

General information about the disease

Doyne honeycomb retinal dystrophy (DHRD) is a rare inherited degenerative disorder affecting the retina. It has early adult onset, starting with small drusen-like spots that progressively expand to form a mosaic pattern described as "honeycomb" (1,2). It is characterized by deposits in the retinal pigment epithelium, geographic atrophy, neovascularization, macular scarring, metamorphopsia, photophobia and vitreous hemorrhage that can lead to progressive loss of visual field and visual acuity (3).

DHRD is considered to be very rare and currently there is insufficient data to estimate its prevalence.

Diagnosis of DHRD is based on clinical findings, ophthalmological examination, electroretinography, fluorescein angiography and optical coherence tomography. It is confirmed by molecular genetic analysis of the responsible gene.

Differential diagnosis should consider other degenerative retinal disorders such as age-related macular dystrophy, early onset macular dystrophy, Best disease, cone-rod dystrophy, and retinitis punctata albescens.

DHRD is inherited in an autosomal dominant manner and the only causative gene is *EFEMP1* (OMIM gene: 601548; OMIM disease: 126600). Therefore, it is important to evaluate the recurrence of the phenotype in the family (family pedigree).

Pathogenic variants may contain splice-site, missense and nonsense variants. Exon or whole-gene duplications/deletions are not usually detected.

Aims of the test

- To determine the gene defect responsible for the pathology;
- To confirm clinical diagnosis of the disease.

Test characteristics

Expert centers/ Published guidelines

The test is listed in the Orphanet database and is offered by 11 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 7 accredited medical genetic laboratories in the US.

Currently there are no guidelines for clinical use of the test.

Test strategy

Sanger sequencing is used for the detection of nucleotide variations in coding exons and flanking introns in the *EFEMP1* gene. Sanger sequencing is also used for family segregation studies.

The test identifies variations in known causative gene in patients suspected to have DHRD. 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 *EFEMP*1 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.

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.

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: Stone et al. analyzed 162 patients with malattia leventinese / Doyne honeycomb retinal dystrophy (ML / DHRD) and 477 controls, identifying the R345W variation in *EFEMP1* in 99% of affected patients (4). In a later study of 29 patients, Michaelides et al. reported the same variation in 86% of cases (5).

Clinical specificity: can be estimated at approximately 99.99% [Author's laboratory data] (6).

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 (7)	yes
Couple risk assessment	yes

References

1. Gregory CY, Evans K, Wijesuriya SD, Kermani S, Jay MR, Plant C, et al. The gene responsible for autosomal dominant Doyne's honeycomb retinal dystrophy (DHRD) maps to chromosome 2p16. Hum Mol Genet. 1996 Jul;5(7):1055-9. PubMed PMID: 8817347.
2. Piguet B, Haimovici R, Bird AC. Dominantly inherited drusen represent more than one disorder: a historical review. Eye (Lond). 1995;9 (Pt 1):34-41. PubMed PMID: 7713248.
3. Zech JC, Zaouche S, Mourier F, Placuchu H, Grange JD, Trepsat C. Macular dystrophy of malattia leventinese. A 25 year follow up. Br J Ophthalmol. 1999 Oct;83(10):1195-6. PubMed PMID: 10636647; PubMed Central PMCID: PMC1722836.
4. Stone EM, Lotery AJ, Munier FL, Héon E, Piguet B, Guymer RH, et al. A single EFEMP1 mutation associated with both Malattia Leventinese and Doyne honeycomb retinal dystrophy. Nat Genet. 1999 Jun;22(2):199-202. PubMed PMID: 10369267.
5. Michaelides M, Jenkins SA, Jr Brantley MA, Andrews RM, Waseem N, Luong V, et al. Maculopathy due to the R345W substitution in fibulin-3: distinct clinical features, disease variability, and extent of retinal dysfunction. Invest Ophthalmol Vis Sci. 2006 Jul;47(7):3085-97. PubMed PMID: 16799055.
6. Chen B, Gagnon M, Shahangian S, Anderson NL, Howerton DA, Boone JD. Good laboratory practices for molecular genetic testing for heritable diseases and conditions. MMWR Recomm Rep. 2009 Jun;58(RR-6):1-37; PubMed PMID: 19521335.
7. Stone EM, Aldave AJ, Drack AV, Maccumber MW, Sheffield VC, Traboulsi E, Weleber RG. Recommendations for genetic testing of inherited eye diseases: report of the American Academy of Ophthalmology task force on genetic testing. Ophthalmology. 2012 Nov;119(11):2408-10. PubMed PMID: 22944025. Epub 2012/09/01.