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Genetic testing for pattern dystrophies

Andi Abeshi[1,2], Pamela Coppola[3], Tommaso Beccari[4], Munis Dundar[5], Maura Di Nicola[6], Francesco Viola[6], Leonardo Colombo[7] and Matteo Bertelli[2,3]

Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of the genetic test for pattern dystrophies. Pattern dystrophies are mostly inherited in an autosomal dominant manner (autosomal recessive transmission is rare). The overall prevalence is currently unknown. Pattern dystrophies are caused by variations in the *BEST1, IMPG1, IMPG2, OTX2, PRPH2* and *CTNNA1* genes. 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.

[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]Department of Clinical Sciences and Community Health, University of Milan, Ophthalmological Unit, IRCCS-Cà Granda Foundation-Ospedale Maggiore Policlinico, Milan, Italy
[7]Department of Ophthalmology, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy

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

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Pattern dystrophies

(other synonyms: patterned dystrophy of retinal pigment epithelium) (Retrieved from OMIM.org)

General information about the disease

Pattern dystrophies are a group of rare clinically and genetically heterogeneous diseases of the macula, characterized by different patterns of pigment deposition in the macular region and associated with heterogeneous symptoms such as metamorphopsia, photophobia, decrease in visual acuity ranging from 20/25 to 20/400, with most in the 20/30 to 20/40 range (1). The symptoms of pattern dystrophies are mild and are typically discovered during routine or unrelated eye examinations (2,3). They are classified into five categories on the basis of the pattern of pigment distribution (3):

- butterfly-shaped pigment dystrophy
- adult-onset foveomacular vitelliform dystrophy (AVMD)
- reticular dystrophy
- multifocal pattern dystrophy simulating Stargardt's disease
- fundus pulverulentus

The prevalence of pattern dystrophies is not known, however AVMD appears to be the most prevalent.

The diagnosis of pattern dystrophies is based on clinical findings, ophthalmological examination, optical coherence tomography, fluorescein angiography, electrooculography and electroretinography. Different genetic variations can cause pattern dystrophies, none of which are diagnostic for a certain pattern. Although genetic tests may help to identify the disease, pattern dystrophy remains a clinical diagnosis (4).

Due to its heterogeneous presentations, differential diagnosis for pattern dystrophies must consider many possibilities, ranging from inherited disorders such as Best disease, cone-rod dystrophy and retinitis pigmentosa to infectious diseases such as syphilitic retinitis, blastomycosis and cysticercosis.

Pattern dystrophies are mainly inherited in an autosomal dominant manner and the main genes involved are *PRPH2* (OMIM gene: 179605; OMIM disease: 169150) associated with almost all pattern dystrophies, *OTX2* (OMIM gene: 600037; OMIM disease: 610125) (5), *CTNNA1* (OMIM gene: 116805; OMIM disease: 608970), associated mainly with butterfly-shaped pigment dystrophy (6) and four genes associated mainly with AVMD: *BEST1* (OMIM gene: 607854; OMIM disease: 153700), *IMPG1 (*OMIM gene: 602870; OMIM disease: 616151) (7), I*MPG2* (OMIM gene: 607056; OMIM disease: 616152) and *PRPH2 (OMIM gene:* 179605; OMIM disease: 608161*)*. In some cases, *IMPG1* and *IMPG2* genes are transmitted with autosomal recessive inheritance.

Pathogenic variants may contain small intragenic deletions/insertions, splice-site, missense and nonsense variations. For *BEST1, IMPG2, PRPH2* and *OTX2* genes, partial or whole gene deletions/duplications are also commonly reported.

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

Expert centers/ Published guidelines

The test is listed in the Orphanet database and is offered by about nine accredited medical genetic laboratories in the EU, and in the GTR database, offered by 10 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 "Genetic and rare disease information center" (rarediseases.info.nih.gov).

Test strategy

A multi-gene NGS panel is used for the detection of nucleotide variations in coding exons and flanking introns in *BEST1*, *CTNNA1*, *IMPG1*, *IMPG2*, *PRPH2* and *OTX2* genes. Potentially causative variants and regions with low coverage are Sanger-sequenced. MLPA is used for detection of duplications and deletions in *BEST1* and *PRPH2* genes. Sanger sequencing is also used for family segregation studies.

The test identifies variations in known causative genes in patients suspected to have pattern dystrophy. 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*, *CTNNA1*, *IMPG1*, *IMPG2*, *PRPH2* and *OTX2* 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)

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: literature data shows variations in the *PRPH2* gene in almost all familial cases of autosomal dominant pattern dystrophies, therefore, the clinical sensitivity can be estimated more than 90% (2,8). Variations in the *OTX2* gene have only recently been described in 2 affected families (5). In AVMD, *BEST1* variations are found in 96% of patients with a positive family history and in 50-70% of sporadic cases (9); variants in *PRPH2* gene account for 10.5% of cases and 8% of negative families for *BEST1* and *PRPH2*, are mutated in *IMPG1* and *IMPG2* genes (10).

Clinical specificity: ranging from 99.95% to 99.99% [Author's laboratory data] (11).

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 (12)	yes
Couple risk assessment	yes

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