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Genetic testing for gyrate atrophy of the choroid and retina

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for gyrate atrophy of the choroid and retina (GACR). GACR is inherited in an autosomal recessive manner, and has a prevalence of 1/50000 in Finland. In the international literature there are approximately 200 biochemically confirmed cases. GACR is caused by mutations in the *OAT* gene. Clinical diagnosis involves ophthalmological examination, electrophysiological testing (electroretinography - ERG), coherence tomography and assay of ornithine levels in body fluids. The genetic test is useful for confirming diagnosis, as well as for differential diagnosis, couple risk assessment and access to clinical trials.

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Gyrate atrophy of the choroid and retina

(other synonyms: GACR; hyperornithinemia with gyrate atrophy of the choroid and retina, HOGA; gyrate atrophy; ornithine aminotransferase deficiency, OAT deficiency; ornithine keto acid aminotransferase deficiency, OKT deficiency; ornithine - delta - aminotransferase deficiency) (Retrieved from OMIM.org)

General information about the disease

Gyrate atrophy of the choroid and retina (GACR) is a rare disease characterized mainly by convoluted atrophy of the choroid and retina, occurring in childhood and manifesting with myopia, early cataract and night blindness. Rare affected subjects have proximal muscle involvement and slight mental retardation; otherwise intelligence is generally normal (1). High phenotypic variability, as well as variable disease progression, is noted among patients even within the same family. There are two distinct genetic forms: one sensitive and the other resistant to pyridoxine. Treatment consists in administration of pyridoxine: sensitive patients respond with normalized blood levels of ornithine and should be treated for the rest of their lives, whereas resistant patients can be treated with a low protein diet (2,3).

The prevalence of GACR in Finland is reported to be 1/50000 with an estimated frequency for heterozygotes of 1 in 110 individuals. The international literature indicates approximately 200 known biochemically confirmed cases of GACR (4).

The diagnosis of GACR is based on clinical findings such as myopia and early cataract, ophthalmological examination showing typical patches of chorioretinal atrophy located circumferentially in the periphery, coherence tomography, ERG evidence of severely reduced amplitudes and ornithine levels in body fluids 10 to 20 times higher than in healthy individuals. Diagnosis is confirmed by detection of pathogenic variants of the gene.

Differential diagnosis should consider X-chromosomal choroideremia, which is determined by blood levels of ornithine and hyperpigmentation of RPE.

OAT deficiency is transmitted as an autosomal recessive character and is caused by variations in the *OAT* gene (OMIM gene: 613349; OMIM disease: 258870) that encodes the mitochondrial aminotransferase ornithine (5). There are about 70 pathogenic variants that may consist in small intragenic deletions/insertions or splice site, missense or nonsense mutations.

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 23 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 15 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).

Test strategy

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

The test identifies variations in known causative genes in patients suspected to have GACR. 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 gene 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 *OAT* 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

The analyzed gene has autosomal recessive 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 gene and disease.

Analytical sensitivity (proportion of positive tests when the genotype is truly present) and 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: more than 70 variations in the *OAT* gene are associated with GACR, but in many cases these are individual variations (identified in one or few families) and total epidemiological data is therefore not available. Clinical sensitivity will be estimated on the basis of internal cases (6).

Clinical specificity: is estimated at approximately 99% (6).

Prescription appropriateness

The genetic test is appropriate when:

a) the patient meets the diagnostic criteria for GACR;

b) the sensitivity of the test is 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

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