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Genetic testing for Refsum disease

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Abstract

We reviewed the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for Refsum disease. The disease has autosomal recessive inheritance, unknown prevalence, and is caused by variations in *PEX7* and *PHYH* genes. Clinical diagnosis is based on clinical findings, ophthalmological examination, electroretinography, optical coherence tomography and phytanic acid assay. The genetic test is useful for confirming diagnosis, for differential diagnosis, couple risk assessment and access to clinical trials.

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Refsum disease

(other synonyms: adult Refsum disease, ARD, classic Refsum disease, CRD, hereditary motor and sensory neuropathy Type IV, heredopathia atactica polyneuritiformis, HMSN IV, HMSN type IV, phytanic acid storage disease, Refsum syndrome, Refsum's disease) (Retrieved from ghr.nlm.nih.gov)

General information about the disease

Refsum Disease (RD) is a rare inherited syndromic disorder affecting the retina, the sense of smell (anosmia) and a wide range of other organs. Its ocular findings include early-onset retinitis pigmentosa (with night blindness as a prominent sign), cataract and nystagmus (1). Other clinical findings include anosmia, polyneuropathy, sensorineural deafness, ataxia and ichthyosis (2,3).

RD is considered a rare disease. Most cases described in the literature are of British or Norwegian origin. Current worldwide prevalence is unknown.

Diagnosis of RD is based on clinical findings, ophthalmological examination, electroretinography, optical coherence tomography and phytanic acid assay, typically increased in RD. The diagnosis is confirmed by molecular genetic analysis of the responsible genes.

Differential diagnosis should first consider retinitis pigmentosa, with which it shares many clinical ocular features, Usher syndrome, alphamethylacyl CoA racemase (AMACR) deficiency (4), Alström syndrome, Bardet Biedl syndrome, Friedreich ataxia and Sjögren Larsson syndrome.

RD has autosomal recessive inheritance and the causative genes are *PHYH* (OMIM gene: 602026; OMIM disease: 266500) and *PEX7* (OMIM gene: 601757; OMIM disease: 614879).

Pathogenic variants may include small intragenic deletions/insertions or 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;
- To determine carrier status for the disease.

The test

Experts centers/Published guidelines

The test is listed in the Orphanet database and is offered by 21 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 13 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" (5).

Test strategy

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

The test identifies variations in known causative genes in patients suspected to have RD. 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 *PEX7* or *PHYH* 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.

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.

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.

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 the *PHYH* gene are identified in more than 90% of patients with Refsum disease, whereas variations in *PEX7* are found in about 10% of cases (5).

Clinical specificity: is 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

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