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Genetic testing for X-linked juvenile retinoschisis

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for X-linked juvenile retinoschisis (XJR). The disease has X-linked inheritance, a prevalence that varies from one in 5000 to one in 25000 males, and is caused by mutations in the *RS1* 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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X-linked juvenile retinoschisis

(other synonyms: RS1, XLRS1, RS, congenital X-linked retinoschisis, degenerative retinoschisis, juvenile retinoschisis, X-linked retinoschisis, XJR) (Retrieved from Orphanet, OMIM.org, Genetics Home Reference)

General information about the disease

X-linked juvenile retinoschisis (XJR) is a rare inherited disorder of the macula affecting males. Onset is typically in early infancy. XJR is characterized by bilateral reduced central visual acuity (from 20/60 in early stages to 20/200 in later stages), strabismus and hyperopia. Other less frequent findings include abnormal pigmentation, atrophy of the retinal pigment epithelium, retinal detachment and vitreous hemorrhage.

The estimated prevalence of XJR varies from one in 5000 to one in 25000 males (1,2).

Diagnosis of XJR is based on clinical findings, ophthalmological examination, electroretinography and optical coherence tomography (3). The diagnosis is confirmed by molecular genetic analysis of the related gene.

Differential diagnosis should consider cystoid macular edema, retinitis pigmentosa, degenerative retinoschisis, retinal detachment, amblyopia and erosive vitreoretinopathy.

XJR has X-linked mode of inheritance and the causative gene is *RS1* (OMIM gene: 300839; OMIM disease: 312700). It has a complete penetrance and variable expressivity.

Pathogenic variants may include small intragenic deletions/insertions, splice-site, missense and nonsense variants; exon or whole-gene duplications/deletions are also typically reported. More than 200 different disease-causing mutations have been reported in the *RS1* gene, approximately 10% of which are deletions (4).

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 11 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 9 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" (2).

Test strategy

Sanger sequencing is used for the detection of nucleotide variations in coding exons and flanking introns in the *RS1* gene. MLPA is used to detect deletions. Sanger sequencing is also used for family segregation studies.

The test identifies variations in known causative genes in patients suspected to have XJR. 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 *RS1* 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:

- 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;
- alterations that cannot be identified by sequencing, such as large rearrangements that cause loss (deletion) or gain (duplication) of extended gene fragments.

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 X-linked transmission, affected males only transmit the disease variant to their daughters. The probability that a female carrier transmits the pathogenic variant to her offspring is 50% in any pregnancy independently of the sex of the conceived. Females who inherit the pathogenic variant will be carriers and usually unaffected. Males who inherit the pathogenic variant will be affected.

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%.

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: in affected males varies from 90 to 96% (2).

Clinical specificity: is estimated at approximately 99.99% [Author's laboratory data] (5).

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 (6)	yes
Couple risk assessment	yes

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