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Genetic testing for Norrie disease

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of genetic testing for Norrie disease. The disease is caused by variations in the *NDP* gene. Its prevalence is currently unknown. Inheritance is X-linked recessive. Clinical diagnosis is based on clinical findings, color vision testing, optical coherence tomography, ophthalmological examination and electroretinography. The genetic test is useful for confirming diagnosis, and for differential diagnosis, couple risk assessment and access to clinical trials.

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Norrie disease

(Other synonyms: Anderson-Warburg syndrome, atrophia bulborum hereditaria, Episkopi blindness, fetal iritis syndrome, Norrie syndrome, Whitnall-Norman syndrome, oligophrenia microphthalmus, congenital pseudoglioma) (retrieved from OMIM.org, ghr.nlm.nih.gov)

General information about the disease

Norrie disease (ND) is a rare inherited vitreoretinal disorder characterized by fibrous and proliferative changes in the retina that can lead to formation of grayish-yellow fibrovascular masses known as pseudogliomas. Individuals with ND may develop blindness at birth or shortly after, cataracts, nystagmus and increased intraocular pressure. Other clinical findings include phthisis bulbi (shrinking of the eyeballs), developmental delay/mental retardation (1) and about 40% develop progressive sensorineural hearing loss beginning in early childhood (2,3).

The prevalence of ND is currently unknown because there have been few publications on this disease.

Diagnosis is based on clinical findings, ophthalmological examination, color vision testing, optical coherence tomography of the retinal pigment epithelium and electroretinography. It is confirmed by detection of pathogenic variants in the causative gene.

Differential diagnosis should consider retinopathy of prematurity (4), retinoblastoma, autosomal dominant familial exudative vitreoretinopathy and persistent hyperplastic primary vitreous.

ND is an X-linked recessive disorder caused by variations in the NDP gene (OMIM gene: 300658; OMIM disease: 310600).

Pathogenic variants may include sequence variations (missense, nonsense, splicing, small insertions and deletions). Partial or whole gene deletions/duplications have also been reported (5-7). Penetrance is complete in affected males, whereas carrier females are generally asymptomatic.

Aims of 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 12 accredited medical genetic laboratories in the EU, and in the GTR database, offered by 11 accredited medical genetic laboratories in the US.

The guidelines for clinical use of the test are described in "Genetics home reference" and "Gene reviews" (8).

Test strategy

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

The test identifies variations in known causative genes in patients suspected to have ND. 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 the NDP 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:

- 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

The gene has X-linked recessive 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: it is estimated that variations in the NDP gene are identified as causative in approximately 95% of cases (8).

Clinical specificity: is estimated at about 99.99% [Author's laboratory data] (9).

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 (10)	yes
Couple risk assessment	yes

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