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Genetic testing for congenital stationary night blindness

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Abstract

We studied the scientific literature and disease guidelines in order to summarize the clinical utility of the genetic test for congenital stationary night blindness (CSNB). CSNB is inherited in an autosomal dominant manner in the case of mutations in the *GNAT1, PDE6B and RHO* genes, in an autosomal recessive manner in the case of mutations in the *CABP4*, *GNB3, GPR179*, *GRM6*, *LRIT3, SAG*, *SLC24A1, TRPM1 and* genes and in an X-linked recessive manner in the case of mutations in the *CACNA1F and NYX* genes. The overall prevalence of CSNB is not known. Clinical diagnosis is based on clinical findings, ophthalmological examination, visual evoked potentials 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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Congenital stationary night blindness

(other synonyms: CSNB congenital stationary night blindness with myopia, myopia-night blindness, hemeralopia-myopia, nyctalopia) (Retrieved from genedx.com)

General information about the disease

Congenital stationary night blindness (acronym CSNB) is a rare group of clinically and genetically heterogeneous nonprogressive retinal disorders characterized by impaired night vision, defective dark adaptation (scotopic ERG defect), reduced visual acuity, myopia, and strabismus, usually with a retina that appears normal to fundus examination (1, 2). CSNB can be divided into two subgroups: "complete" (associated with the *NYX* and *TRPM1* genes) and "incomplete," defined by the presence or absence of residual rod function as assessed by dark adaptometry or electroretinography (ERG) (3). The vision problems are present from birth and tend to remain stable in time. The prevalence of CSNB is not known, however the X-linked form appears to be more prevalent in persons of Dutch-German Mennonite descent, where a founder effect has been reported (4-6).

The diagnosis of CSNB is based on clinical findings, ophthalmological examination, visual evoked potentials (typically absent or delayed) and electroretinography (reduced oscillatory potentials) (7). It is confirmed by detection of pathogenic gene variants.

Differential diagnosis should consider normal fundus disorders such as blue cone monochromacy, X-linked motor nystagmus and abnormal fundus disorders such as ocular albinism and X-linked juvenile retinoschisis.

The CSNB may be transmitted as an autosomal recessive trait associated with variations in the *CABP4* (OMIM gene: 608965; OMIM disease: 610427), *GNB3* (OMIM gene: 139130; OMIM disease: 617024), *GPR179* (OMIM gene: 614515; OMIM disease: 614565), *GRM6* (OMIM gene: 604096; OMIM disease: 257270), *LRIT3* (OMIM gene: 615004; OMIM disease: 615058), *SAG* (OMIM gene: 181031; OMIM disease: 258100), *SLC24A1* (OMIM gene:

603617; OMIM disease: 613830) and *TRPM1* (OMIM gene: 603576; OMIM disease: 613216) genes, as an autosomal dominant trait associated with variations in the *GNAT1* (OMIM gene: 139330; OMIM disease: 610444), *PDE6B* (OMIM gene: 180072; OMIM disease: 163500) and *RHO* (OMIM gene: 180380; OMIM disease: 610445) genes or as an X-linked recessive trait associated with variations in the *CACNA1F* (OMIM gene: 300110; OMIM disease: 300071) and *NYX* (OMIM gene: 300278; OMIM disease: 310500) genes. Penetrance of X-linked forms is probably 100%, but expressivity is variable (6); little data is available about the penetrance and expressivity of the other forms. Pathogenic variants may include small intragenic deletions/insertions, splice-site, missense or nonsense variations. For *CABP4*, *SAG*, *SLC24A1, TRPM1*, *PDE6B*, *RHO*, *CACNA1F* and *NYX* 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, for genes with recessive autosomal/ X-linked inheritance.

Test characteristics

Expert centers/ Published guidelines

The test is listed in the Orphanet database and is offered by 14 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" (8).

Test strategy

A multi-gene NGS panel is used for the detection of nucleotide variations in coding exons and flanking introns in the *CABP4*, *GNB3*, *GPR179*, *GRM6*, *LRIT3*, *SAG*, *SLC24A1*, *TRPM1*, *GNAT1*, *PDE6B*, *RHO*, *CACNA1F* and *NYX* genes. Potentially causative variants and regions with low coverage are Sanger-sequenced. MLPA is used for detection of duplications and deletions in the *RHO* gene. Sanger sequencing is also used for family segregation studies.

The test identifies variations in known causative genes in patients suspected to have CSNB. 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 *CABP4*, *GNB3, GPR179*, *GRM6*, *LRIT3, SAG*, *SLC24A1, TRPM1, GNAT1, PDE6B, RHO, CACNA1F* or *NYX* genes 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%.

Recessive X linked inheritance: 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)

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: overall, the analysis of associated genes can reach a diagnostic sensitivity of about 50%. X-linked forms account for 57.9% of cases, autosomal recessive and sporadic forms for 40%, and autosomal dominant forms for 2.1% (9).

Clinical specificity: can be estimated at approximately 99.99% [Author's laboratory data] (10).

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 (11)	yes
Couple risk assessment	yes

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