GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

X-Linked Congenital Stationary Night Blindness

[*X-Linked CSNB. Includes: CACNA1F-Related X-Linked Congenital Stationary Night Blindness (CSNB2), NYX-Related X-Linked Congenital Stationary Night Blindness (CSNB1)*]

Kym M Boycott, PhD, MD
Clinical Geneticist, Department of Genetics
Children's Hospital of Eastern Ontario
Assistant Professor, Department of Pediatrics
University of Ottawa
kboycott@cheo.on.ca

N Torben Bech-Hansen, PhD
Roy and Joan Allen Professor in Sight Research
Departments of Medical Genetics and Surgery
University of Calgary
ntbech@ucalgary.ca

Yves Sauvé, PhD
Departments of Ophthalmology and Physiology
University of Alberta
ysauve@ualberta.ca

Ian M MacDonald, MD, CM
Branch Chief, Ophthalmic Genetics
National Eye Institute
National Institutes of Health
macdonaldi@nei.nih.gov

Initial Posting: January 16, 2008.

Summary

Disease characteristics. X-linked congenital stationary night blindness (CSNB) is characterized by non-progressive retinal findings of reduced visual acuity ranging from 20/30 to 20/200; defective dark adaptation; refractive error (most typically myopia ranging from low [-0.25 diopters (D) to -4.75 D] to high [≥-10.00 D] but occasionally hyperopia); nystagmus; strabismus; normal color vision; and normal fundus examination. Two slightly different phenotypes are recognized: complete (CSNB1) caused by mutations in *NYX* (45%) and incomplete (CSNB2) caused by mutations in *CACNA1F* (55%).

Diagnosis/testing. Diagnosis is based on clinical findings, characteristic findings on electroretinography (ERG), family history, and molecular genetic testing. *NYX* and *CACNA1F* are the only two genes known to be associated with X-linked CSNB. Molecular genetic testing is available on a clinical basis.

Management. *Treatment of manifestations:* glasses or contact lenses to treat refractive error (myopia or hyperopia). *Prevention of secondary complications:* on occasion, strabismus surgery to improve functional range of null point. *Surveillance:* at a young age yearly eye examinations with refraction to identify and treat myopia as early as possible. *Agents/ circumstances to avoid:* Reduced visual acuity and difficulties seeing at night may preclude driving a car or restrict the class of driving license.

Genetic counseling. X-linked CSNB is inherited in an X-linked manner. The father of an affected male will not have X-linked CSNB nor will he be a carrier of the disease-causing mutation. If the mother of the proband is a carrier, the chance of transmitting the disease-causing mutation in each pregnancy is 50%. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers and will usually not be affected. Males with X-linked CSNB will pass the disease-causing mutation to all of their daughters and none of their sons. Carrier testing for at-risk relatives is possible if the disease-causing mutation in the family is known. No laboratories offering prenatal diagnosis for X-linked CSNB are listed in the GeneTests Laboratory Directory; however, prenatal testing may be available through laboratories offering custom prenatal testing for families in which the disease-causing mutation has been identified.

Diagnosis

Clinical Diagnosis

Affected Males

A clinical diagnosis of X-linked congenital stationary night blindness (X-linked CSNB) can be made in a male with the following findings:

Reduced visual acuity. Vision is reduced in all affected males in the range of 20/30 (6/9; log MAR 0.1) to 20/200 (6/60; log MAR 1.0).

History of defective dark adaptation. Night blindness is a subjective finding; see Characteristic findings on electroretinography (ERG; see below) for explanation of CSNB types 1 and 2.

- Individuals with CSNB1 generally report severe night blindness.
- Individuals with CSNB2 do not uniformly report severe night blindness.

Myopia. Myopia may range from low (-0.25 diopters [D] to -4.75 D) to high (≥ -10.00 D) [Boycott et al 2000, Allen et al 2003]. A few affected individuals have hyperopia.

Nystagmus and strabismus. Fifty percent to 70% of affected individuals have nystagmus and strabismus [Boycott et al 2000, Allen et al 2003].
In a large Mennonite cohort with incomplete X-linked CSNB, at least one of the following was **not** present in 72% of cases: myopia, nystagmus, or night blindness [Boycott et al 2000].

Normal color vision. However, individuals with a severe X-linked CSNB may show mild color vision deficits.

Normal fundus examination. However, persons with high myopia may show myopic degeneration.

Family history consistent with X-linked inheritance

Characteristic findings on ERG. ERG is used to assess the changes in electrical activity of the retina in response to light. The b-wave is caused by the depolarization of ON bipolar cells in response to light stimuli and is strictly dependent on synaptic transmission from photoreceptors to ON bipolar cells.

Individuals with X-linked CSNB have reduced scotopic b-wave amplitudes in response to bright flashes after dark adaptation (Figure 1). The resulting ERG waveform is essentially a

negative wave (amplitude of the a-wave is larger than that of the b-wave) [Miyake et al 1986], referred to as the Schubert-Bornschein form [Schubert & Bornschein 1952].

Based primarily on the results of the scotopic ERG, X-linked CSNB may be further differentiated as follows:

- Complete X-linked CSNB (CSNB1): b-wave is severely reduced or not measurable (i.e., absent).
- Incomplete X-linked CSNB (CSNB2): b-wave is reduced but measurable.

The ERG can define specific retinal dysfunctions and, in general, differentiate the forms of X-linked CSNB (Table 1) to identify the gene most likely to be involved (see Testing Strategy).

Table 1. ERG Findings in Complete and Incomplete X-Linked CSNB

ERG Finding	Complete (CSNB1)	Incomplete (CSNB2)
Scotopic rod b-wave	Severely reduced or absent	Reduced
Mixed scotopic a-wave	Normal	Slightly reduced
Mixed scotopic b-wave	Reduced	Reduced
Scotopic OP	Absent	Slightly reduced
Photopic a-wave	Normal, slightly reduced, saw-tooth (square) shaped	Reduced
Photopic b-wave	Slightly reduced	Reduced
Photopic OP	Lost, except for OP4	All are lost
30-Hz flicker	Normal/slightly reduced	Reduced with double peak

OP = oscillatory potential

Note: Pupillary responses have been described as "paradoxical" in the literature and textbooks (i.e., miosis of pupils when lights are turned off, as opposed to dilation). This description predates genotyping. In 17 individuals with incomplete X-linked CSNB ages five to 51 years examined by one of the authors, none clearly demonstrated a paradoxical papillary response. Further clarification of the presence or absence of this phenomenon in individuals with X-linked CSNB may require measurement with pupillometry.

Carrier Females

In general, carrier females do not exhibit clinical signs of X-linked CSNB; however, on occasion there have been reports of females who are homozygous for mutations in *CACNA1F* with signs similar to those in males [Bech-Hansen et al 1998].

ERG changes that may be observed in obligate carriers of X-linked CSNB:

- Reduced oscillatory potentials (OPs) associated with rod activity [Rigaudière et al 2003]
- Reduced photopic b-wave and flicker amplitudes (with unaffected OPs) in one person [Rigaudière et al 2003]

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. To date, mutations in two genes are known to be associated with X-linked CSNB:

- ***NYX.*** Associated with the clinical phenotype CSNB1 [Bech-Hansen et al 2000, Pusch et al 2000]
- ***CACNA1F.*** Associated with the clinical phenotype CSNB2 [Bech-Hansen et al 1998, Strom et al 1998]

Clinical testing

- **Targeted mutation analysis** is used to identify the *CACNA1F* mutation c. 3167_3168dupC present in the Dutch-German Mennonite population [Bech-Hansen et al 1998, Boycott et al 2000].
- **Sequence analysis** is available on a clinical basis for both *CACNA1F* and *NYX*.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in X-Linked Congenital Stationary Night Blindness

Gene Symbol	Proportion of X-Linked CSNB Attributed to Mutations in This Gene[1]	Test Method	Mutations Detected	Mutation Detection Frequency by Gene and Test Method	Test Availability
NYX	45%	Sequence analysis [2]	*NYX* sequence variants	Unknown	Clinical Testing
		Deletion testing [3]	*NYX* exonic and whole gene deletions [2]		
CACNA1F	55%	Targeted mutation analysis	c.3167_3168dupC	Unknown	Clinical Testing
		Sequence analysis [2]	*CACNA1F* sequence variants		

1. Zeitz [2007]

2. Sequence analysis cannot detect exonic and whole gene deletions in female carriers.
3. A variety of methods may be used including (but not limited to) MLPA and quantitative PCR.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To establish the diagnosis in a proband. A male with reduced visual acuity, myopia, nystagmus, strabismus, and normal color vision may be suspected of having X-linked CSNB. In general, the diagnosis of X-linked CSNB can be made by ophthalmologic examination (including electroretinography) and family history consistent with X-linked inheritance.

To confirm the diagnosis in a proband. Electroretinographic findings can be used to differentiate between CSNB1 and CSNB2 and can direct molecular genetic testing to the appropriate gene (see Table 1).

For individuals of Dutch-German Mennonite descent and features of CSNB2, targeted mutation analysis of the founder mutation in *CACNA1F* can be performed.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this X-linked disorder and may develop some related findings.

Genetically Related (Allelic) Disorders

NYX. One other phenotype may be associated with mutations in *NYX*:

- **High myopia** in two unrelated males was associated with two novel missense mutations in *NYX*, suggesting that mutations in *NYX* may contribute to high myopia without additional features of X-linked CSNB [Zhang et al 2007]. This observation needs to be substantiated by further studies.

CACNA1F. Four other retinal phenotypes inherited in an X-linked manner are associated with mutations in *CACNA1F*:

- **Åland Island eye disease (AIED),** also known as Forsius-Eriksson syndrome, is a retinal disorder characterized by fundus hypopigmentation, decreased visual acuity, nystagmus, astigmatism, protan color vision defect (see Red-Green Color Vision Defects), progressive myopia, and defective dark adaptation. ERG reveals abnormalities in both photopic and scotopic functions. The phenotypic overlap between AIED and CSNB2 is significant. A novel mutation in *CACNA1F* has been identified in affected individuals from the original family with AIED [Jalkanen et al 2007].
- **X-linked cone-rod dystrophy (CORDX3)** is characterized by modest progressive dysfunction of photoreceptors and several features of CSNB2. A mutation in *CACNA1F* has been identified in one Finnish family [Jalkanen et al 2006].
- **X-linked retinal disorder,** described in a large Maori family [Hope et al 2005], shows clinical and ERG similarities to CSNB2 but, in addition, is associated with intellectual disability and manifestations in female carriers (attributed to a unique gain-of-function missense mutation in *CACNA1F* [Hemara-Wahanui et al 2005]).
- **Retinal and optic atrophy,** associated with progressive visual decline, has been described in two Japanese brothers [Nakamura et al 2003].

Clinical Description

Natural History

X-linked congenital stationary night blindness (CSNB) is a congenital non-progressive retinal disorder characterized by defective night vision; reduced visual acuity; myopia; nystagmus; and strabismus (see Clinical Diagnosis).

Genotype-Phenotype Correlations

CSNB1, the complete form of X-linked CSNB, is caused by mutations in *NYX* [Bech-Hansen et al 2000, Pusch et al 2000].

CSNB2, the incomplete form of X-linked CSNB, is caused by mutations in *CACNA1F* [Bech-Hansen et al 1998, Strom et al 1998].

Penetrance

Penetrance of CSNB1 and CSNB2 is probably 100%, but expressivity is variable [Boycott et al 2000]; clinically mild cases may be missed if electroretinography is not performed.

Nomenclature

X-linked CSNB has been referred to in the past as Schubert-Bornschein CSNB, which is a reference to the characteristic "negative" waveform (a-wave larger than the b-wave) of the ERG seen in both X-linked forms of CSNB [Schubert & Bornschein 1952].

The terms CSNB1 and CSNB2 are sometimes used as abbreviations for complete and incomplete CSNB irrespective of the mode of inheritance; originally the terms referred to the two X-linked entities of CSNB.

Prevalence

The prevalence of X-linked CSNB is not known.

A founder effect has been reported in individuals with CSNB2 who are Dutch-German Mennonite descent [Bech-Hansen et al 1998, Boycott et al 1998, Boycott et al 2000].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Normal Fundus

X-linked congenital stationary night blindness (X-linked CSNB) is characterized by a normal fundus. Only a few conditions may initially be confused with the X-linked form of CSNB:

CSNB (non X-linked). Family history consistent with X-linked inheritance may differentiate the X-linked forms of CSNB from the autosomal dominant and recessive forms.

Non-X-linked CSNB is a heterogeneous group of disorders caused by mutations in the following genes:

- **Autosomal dominant**
  - *GNAT1*, the gene encoding the alpha-subunit of rod transducin, (Nougaret-type CSNB) [Dryja et al 1996]
  - *PDE6B*, the gene encoding the beta-subunit of rod cGMP phosphodiesterase [Gal et al 1994]
  - *RHO*, the gene encoding the rhodopsin protein [Dryja et al 1993]
- **Autosomal recessive**
  - *CABP4*, the gene encoding rhodopsin photoreceptor-specific calcium-binding protein [Zeitz et al 2006]
  - *GRM6*, the gene encoding metabotropic glutamate receptor 6 [Dryja et al 2005, Zeitz et al 2005b]

Blue cone monochromacy, inherited in an X-linked manner, is characterized by poor vision and nystagmus. This condition differs clinically from X-linked CSNB in the following ways:

- Color vision testing is abnormal.
- ERG reveals almost completely abolished photopic ERG contrasting with normal or minimally affected scotopic ERG.
- Whereas fundus examination in young males is normal, some males develop macular atrophy in late adulthood.

Blue cone monochromacy results from alterations in the locus control region of the red and green pigment genes. (See Red-Green Color Vision Defects.)

X-linked motor nystagmus can be distinguished from X-linked CSNB by the finding of normal ERG. Mutations in *FRMD7* are causative [Tarpey et al 2006].

Abnormal Fundus

A few conditions with an abnormal fundus examination and an X-linked pattern of inheritance could be confused with X-linked CSNB.

- **X-linked ocular albinism**. Clinical features of iris transillumination and foveal hypoplasia are present in X-linked ocular albinism and not in CSNB. The ERG in X-linked ocular albinism does not show the selective reduction in the amplitude of the b-wave observed in X-linked CSNB. In X-linked ocular albinism the visual evoked potential (VEP) responses show a propensity for more crossing fibers than expected at the level of the chiasm. Mutations in *OA1* are causative.
- **X-linked juvenile retinoschisis**. Visual acuity in X-linked juvenile retinoschisis is reduced to the same range seen in X-linked CSNB. Fundus examination shows foveal schisis or foveal findings in virtually all affected males and approximately 50% have areas of peripheral retinoschisis, neither of which finding is seen in X-linked CSNB. In X-linked juvenile retinoschisis the ERG shows a selective reduction in the amplitude of the b-wave. Mutations in *RS1* are causative.

The following autosomal recessive conditions, also characterized by abnormal fundus, are included here as they are non-progressive and considered part of the spectrum of differential diagnoses of X-linked CSNB:

- **Oguchi disease** is a form of CSNB reported in the Japanese that is caused by mutations in either *SAG*, the gene encoding arrestin, or *GRK1*, the gene encoding rhodopsin kinase. The fundus has an abnormal color, which becomes normal with prolonged dark adaptation (the Mizuo phenomenon) [Dryja 2000].
- **Fundus albipunctatus** is a form of CSNB caused by mutations in *RDH5*, the gene encoding retinol dehydrogenase. The fundus shows discretely scattered white retinal dots. The ERG, when recorded under standard conditions, shows selective reduction in the b-wave, which normalizes with prolonged dark adaptation [Dryja 2000].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with X-linked congenital stationary night blindness (CSNB), the following evaluations are recommended:

- Ophthalmologic examination
- Electroretinography
- Family history
- Dark adaptation (optional)

Treatment of Manifestations

Coincident high myopia or hyperopia can be managed with glasses or contact lenses.

Prevention of Secondary Complications

In some cases, a boy with X-linked CSNB may adopt a cosmetically unacceptable or functionally awkward head posture to dampen the degree of nystagmus in a particular position of gaze (the so-called "null point"). In some instances the position of gaze for the null point may be shifted to a better functional range by carefully planned strabismus surgery.

Surveillance

Regular (yearly) eye examinations are recommended with refraction at a young age to monitor for the development of myopia.

Agents/Circumstances to Avoid

Reduced visual acuity and difficulties seeing at night may preclude driving a car or restrict the class of driving license.

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

X-linked congenital stationary night blindness (CSNB) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have X-linked CSNB nor will he be a carrier of the disease-causing mutation.

- In a family with more than one affected male, the mother of an affected male is an obligate carrier.
- Possible genetic explanations for a male proband with no family history of X-linked CSNB (i.e., a simplex case):
  - He has a *de novo* mutation and his mother is not a carrier.
  - His mother has a *de novo* mutation either (a) as a "germline mutation" (i.e., present at the time of her conception and therefore in every cell of her body); or (b) as "germline mosaicism" (i.e., present in some of her germ cells only). Germline mosaicism has not been reported in individuals with X-linked CSNB, but it has been observed in many X-linked disorders and should be considered in the genetic counseling of at-risk family members. In both instances [(a) and (b)], other offspring of the proband's mother are at risk of inheriting the mutation; however, the sibs of the proband's mother are not at risk of having inherited the altered gene.
  - His mother has a mutation that she inherited from a maternal female ancestor.

Sibs of a proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother of the proband has an altered allele, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers and will usually not be affected. Rare cases do occur where a female is affected, having inherited two mutant alleles, one from a carrier mother and one from an affected father.
- If the altered allele cannot be detected in the DNA of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Males with X-linked CSNB will pass the altered allele to all of their daughters and none of their sons.

Other family members of a proband. The proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their gender, may be at risk of being carriers or of having X-linked CSNB.

Carrier Detection

Carrier testing of at-risk female relatives is available on a clinical basis if the disease-causing mutation has been identified in the family.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and clarification of carrier status is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or carriers.

DNA Banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methods and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100% or molecular genetic

testing is primarily available on a research basis only. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

No laboratories listed in the GeneTests Laboratory Directory or on the Human Genetics Quality Network Web site (www.hgqn.org) offer molecular genetic testing for prenatal diagnosis of X-linked CSNB. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as X-linked CSNB that do not affect intellect or life span are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the altered allele has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of X-Linked Congenital Stationary Night Blindness

Gene Symbol	Chromosomal Locus	Protein Name
CACNA1F	Xp11.2	Voltage-dependent L-type calcium channel subunit alpha-1F
NYX	Xp11.4	Nyctalopin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for X-Linked Congenital Stationary Night Blindness

300071	NIGHT BLINDNESS, CONGENITAL STATIONARY, TYPE 2A; CSNB2A
300110	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, ALPHA-1F SUBUNIT; CACNA1F
300278	NYCTALOPIN; NYX
310500	NIGHT BLINDNESS, CONGENITAL STATIONARY, TYPE 1A; CSNB1A

Table C. Genomic Databases for X-Linked Congenital Stationary Night Blindness

Gene Symbol	Locus Specific	Entrez Gene	HGMD
CACNA1F	CACNA1F	778 (MIM No. 300110)	CACNA1F
NYX	NYX	60506 (MIM No. 300278)	NYX

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Genes associated with X-linked congenital stationary night blindness (X-linked CSNB) encode proteins that are specifically expressed in the retina: nyctalopin and voltage-dependent L-type

calcium channel subunit alpha-1F ($Ca_v1.4/\alpha_{1F}$) for complete and incomplete CSNB, respectively. Mutations identified in these genes impinge on synaptic transmission from photoreceptors (rods and cones) to inner retinal cells.

NYX

Normal allelic variants: *NYX* spans approximately 28 kb of genomic DNA and contains three exons.

Pathologic allelic variants: The mutation spectrum is wide, including missense, nonsense, and splice site mutations, deletions, and insertions. More than 50% of the mutations documented have been missense [Zeitz et al 2005a, Zeitz 2007].

Normal gene product: *NYX* encodes nyctalopin, a protein of 481 amino acids in the small leucine-rich proteoglycan family. Nyctalopin contains a signal peptide, a set of 12 leucine-rich repeats, and a glycosylphosphatidylinositol (GPI)-anchoring sequence [Bech-Hansen et al 2000, Pusch et al 2000, Bech-Hansen et al 2005].

Abnormal gene product: Mutations in *NYX* are predicted to cause a number of functional defects in nyctalopin, including alterations in its conformation, loss of the GPI anchor, and deletions of a portion or all of the protein [Zeitz 2007].

CACNA1F

Normal allelic variants: *CACNA1F* spans approximately 28 kb of genomic DNA and contains 48 exons.

Pathologic allelic variants: See Table 3. The mutation spectrum is wide, including missense, nonsense, and splice site mutations, deletions, and insertions. More than 50% of the mutations identified have been nonsense [Zeitz et al 2005a,Zeitz 2007].

Table 3. *CACNA1F* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change (Alias [1])	Reference Sequence
c.3167_3168dupC (3166dupC)	p.Leu1056ProfsX11 (Leu991insC)	NM_005183.2

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

Normal gene product: *CACNA1F* encodes a protein in which one of the splice isoforms has 1966 amino acids ($Ca_v1.4/\alpha_{1F}$) and is a voltage-gated L-type calcium channel [Bech-Hansen et al 1998, Strom et al 1998].

Abnormal gene product: Expression studies have shown that some (not all) *CACNA1F* missense mutations alter the channel activation properties of the $Ca_v1.4$ calcium channel [McRory et al 2004, Hemara-Wahanui et al 2005, Hoda et al 2005]; other missense mutations may affect the assembly or expression of the presynaptic ribbon complex [Hoda et al 2006]. Nonsense and frameshift mutations are predicted to cause loss of channel function or/and photoreceptor synapses.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other

organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Foundation Fighting Blindness
11435 Cronhill Drive
Owings Mill MD 21117-2220
Phone: 888-394-3937 (toll-free); 800-683-5555 (toll-free TDD); 410-568-0150 (local)
Email: info@blindness.org
www.blindness.org

Foundation Fighting Blindness–Canada
890 Yonge Street 12th Floor
Toronto M4W 3P4
Canada
Phone: 800-461-3331 (toll-free); 416-360-4200
Fax: 416-360-0060
Email: info@ffb.ca
www.ffb.ca

National Eye Institute
Low Vision

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Allen LE, Zito I, Bradshaw K, Patel RJ, Bird AC, Fitzke F, Yates JR, Trump D, Hardcastle AJ, Moore AT. Genotype-phenotype correlation in British families with X linked congenital stationary night blindness. *Br J Ophthalmol* 2003;87:1413–20. [PubMed: 14609846]

Bech-Hansen NT, Cockfield J, Liu D, Logan CC. Isolation and characterization of the leucine-rich proteoglycan nyctalopin gene (cNyx) from chick. *Mamm Genome* 2005;16:815–24. [PubMed: 16261423]

Bech-Hansen NT, Naylor MJ, Maybaum TA, Pearce WG, Koop B, Fishman GA, Mets M, Musarella MA, Boycott KM. Loss-of-function mutations in a calcium-channel alpha1-subunit gene in Xp11.23 cause incomplete X-linked congenital stationary night blindness. *Nat Genet* 1998;19:264–7. [PubMed: 9662400]

Bech-Hansen NT, Naylor MJ, Maybaum TA, Sparkes RL, Koop B, Birch DG, Bergen AA, Prinsen CF, Polomeno RC, Gal A, Drack AV, Musarella MA, Jacobson SG, Young RS, Weleber RG. Mutations in NYX, encoding the leucine-rich proteoglycan nyctalopin, cause X-linked complete congenital stationary night blindness. *Nat Genet* 2000;26:319–23. [PubMed: 11062471]

Boycott KM, Pearce WG, Bech-Hansen NT. Clinical variability among patients with incomplete X-linked congenital stationary night blindness and a founder mutation in CACNA1F. *Can J Ophthalmol* 2000;35:204–13. [PubMed: 10900517]

Boycott KM, Pearce WG, Musarella MA, Weleber RG, Maybaum TA, Birch DG, Miyake Y, Young RS, Bech-Hansen NT. Evidence for genetic heterogeneity in X-linked congenital stationary night blindness. *Am J Hum Genet* 1998;62:865–75. [PubMed: 9529339]

Dryja TP. Molecular genetics of Oguchi disease, fundus albipunctatus, and other forms of stationary night blindness: LVII Edward Jackson Memorial Lecture. *Am J Ophthalmol* 2000;130:547–63. [PubMed: 11078833]

Dryja TP, Berson EL, Rao VR, Oprian DD. Heterozygous missense mutation in the rhodopsin gene as a cause of congenital stationary night blindness. *Nat Genet* 1993;4:280–3. [PubMed: 8358437]

Dryja TP, Hahn LB, Reboul T, Arnaud B. Missense mutation in the gene encoding the alpha subunit of rod transducin in the Nougaret form of congenital stationary night blindness. *Nat Genet* 1996;13:358–60. [PubMed: 8673138]

Dryja TP, McGee TL, Berson EL, Fishman GA, Sandberg MA, Alexander KR, Derlacki DJ, Rajagopalan AS. Night blindness and abnormal cone electroretinogram ON responses in patients with mutations in the GRM6 gene encoding mGluR6. *Proc Natl Acad Sci U S A* 2005;102:4884–9. [PubMed: 15781871]

Gal A, Orth U, Baehr W, Schwinger E, Rosenberg T. Heterozygous missense mutation in the rod cGMP phosphodiesterase beta-subunit gene in autosomal dominant stationary night blindness. *Nat Genet* 1994;7:64–8. [PubMed: 8075643]

Hemara-Wahanui A, Berjukow S, Hope CI, Dearden PK, Wu SB, Wilson-Wheeler J, Sharp DM, Lundon-Treweek P, Clover GM, Hoda JC, Striessnig J, Marksteiner R, Hering S, Maw MA. A CACNA1F mutation identified in an X-linked retinal disorder shifts the voltage dependence of Cav1.4 channel activation. *Proc Natl Acad Sci U S A* 2005;102:7553–8. [PubMed: 15897456]

Hoda JC, Zaghetto F, Koschak A, Striessnig J. Congenital stationary night blindness type 2 mutations S229P, G369D, L1068P, and W1440X alter channel gating or functional expression of Ca(v)1.4 L-type Ca2+ channels. *J Neurosci* 2005;25:252–9. [PubMed: 15634789]

Hoda JC, Zaghetto F, Singh A, Koschak A, Striessnig J. Effects of congenital stationary night blindness type 2 mutations R508Q and L1364H on Cav1.4 L-type Ca2+ channel function and expression. *J Neurochem* 2006;96:1648–58. [PubMed: 16476079]

Hope CI, Sharp DM, Hemara-Wahanui A, Sissingh JI, Lundon P, Mitchell EA, Maw MA, Clover GM. Clinical manifestations of a unique X-linked retinal disorder in a large New Zealand family with a novel mutation in CACNA1F, the gene responsible for CSNB2. *Clin Experiment Ophthalmol* 2005;33:129–36. [PubMed: 15807819]

Jalkanen R, Bech-Hansen NT, Tobias R, Sankila EM, Mantyjarvi M, Forsius H, de la Chapelle A, Alitalo T. A novel CACNA1F gene mutation causes Aland Island eye disease. *Invest Ophthalmol Vis Sci* 2007;48:2498–502. [PubMed: 17525176]

Jalkanen R, Mantyjarvi M, Tobias R, Isosomppi J, Sankila EM, Alitalo T, Bech-Hansen NT. X linked cone-rod dystrophy, CORDX3, is caused by a mutation in the CACNA1F gene. *J Med Genet* 2006;43:699–704. [PubMed: 16505158]

McRory JE, Hamid J, Doering CJ, Garcia E, Parker R, Hamming K, Chen L, Hildebrand M, Beedle AM, Feldcamp L, Zamponi GW, Snutch TP. The CACNA1F gene encodes an L-type calcium channel with unique biophysical properties and tissue distribution. *J Neurosci* 2004;24:1707–18. [PubMed: 14973233]

Miyake Y, Yagasaki K, Horiguchi M, Kawase Y, Kanda T. Congenital stationary night blindness with negative electroretinogram. A new classification. *Arch Ophthalmol* 1986;104:1013–20. [PubMed: 3488053]

Nakamura M, Ito S, Piao CH, Terasaki H, Miyake Y. Retinal and optic disc atrophy associated with a CACNA1F mutation in a Japanese family. *Arch Ophthalmol* 2003;121:1028–33. [PubMed: 12860808]

Pusch CM, Zeitz C, Brandau O, Pesch K, Achatz H, Feil S, Scharfe C, Maurer J, Jacobi FK, Pinckers A, Andreasson S, Hardcastle A, Wissinger B, Berger W, Meindl A. The complete form of X-linked congenital stationary night blindness is caused by mutations in a gene encoding a leucine-rich repeat protein. *Nat Genet* 2000;26:324–7. [PubMed: 11062472]

Rigaudière F, Roux C, Lachapelle P, Rosolen SG, Bitoun P, Gay-Duval A, Le Gargasson JF. ERGs in female carriers of incomplete congenital stationary night blindness (I-CSNB). A family report. *Doc Ophthalmol* 2003;107:203–12. [PubMed: 14661912]

Schubert G, Bornschein H. Analysis of the human electroretinogram. *Ophthalmologica* 1952;123:396–413. [PubMed: 14957416]

Strom TM, Nyakatura G, Apfelstedt-Sylla E, Hellebrand H, Lorenz B, Weber BH, Wutz K, Gutwillinger N, Ruther K, Drescher B, Sauer C, Zrenner E, Meitinger T, Rosenthal A, Meindl A. An L-type calcium-channel gene mutated in incomplete X-linked congenital stationary night blindness. *Nat Genet* 1998;19:260–3. [PubMed: 9662399]

Tarpey P, Thomas S, Sarvananthan N, Mallya U, Lisgo S, Talbot CJ, Roberts EO, Awan M, Surendran M, McLean RJ, Reinecke RD, Langmann A, Lindner S, Koch M, Jain S, Woodruff G, Gale RP, Degg C, Droutsas K, Asproudis I, Zubcov AA, Pieh C, Veal CD, Machado RD, Backhouse OC, Baumber L, Constantinescu CS, Brodsky MC, Hunter DG, Hertle RW, Read RJ, Edkins S, O'Meara S, Parker A, Stevens C, Teague J, Wooster R, Futreal PA, Trembath RC, Stratton MR, Raymond FL, Gottlob I. Mutations in FRMD7, a newly identified member of the FERM family, cause X-linked idiopathic congenital nystagmus. *Nat Genet* 2006;38:1242–4. [PubMed: 17013395]

Zeitz C. Molecular genetics and protein function involved in nocturnal vision. *Exp Rev Ophthalmol* 2007;2:467–85.

Zeitz C, Kloeckener-Gruissem B, Forster U, Kohl S, Magyar I, Wissinger B, Matyas G, Borruat FX, Schorderet DF, Zrenner E, Munier FL, Berger W. Mutations in CABP4, the gene encoding the Ca2 +-binding protein 4, cause autosomal recessive night blindness. *Am J Hum Genet* 2006;79:657–67. [PubMed: 16960802]

Zeitz C, Minotti R, Feil S, Matyas G, Cremers FP, Hoyng CB, Berger W. Novel mutations in CACNA1F and NYX in Dutch families with X-linked congenital stationary night blindness. *Mol Vis* 2005a; 11:179–83. [PubMed: 15761389]

Zeitz C, van Genderen M, Neidhardt J, Luhmann UF, Hoeben F, Forster U, Wycisk K, Matyas G, Hoyng CB, Riemslag F, Meire F, Cremers FP, Berger W. Mutations in GRM6 cause autosomal recessive congenital stationary night blindness with a distinctive scotopic 15-Hz flicker electroretinogram. *Invest Ophthalmol Vis Sci* 2005b;46:4328–35. [PubMed: 16249515]

Zhang Q, Xiao X, Li S, Jia X, Yang Z, Huang S, Caruso RC, Guan T, Sergeev Y, Guo X, Hejtmancik JF. Mutations in NYX of individuals with high myopia, but without night blindness. *Mol Vis* 2007;13:330–6. [PubMed: 17392683]

Suggested Reading

Dryja TP. Retinitis pigmentosa and stationary night blindness. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 235. Available at www.ommbid.com. Accessed 1-14-08.

Miyake Y (2006) Congenital stationary blindness. In: Heckenlively JR and Arden GB (eds) Principles and Practice of Clinical Electrophysiology of Vision, 2 ed. MIT Press, Cambridge, MA, pp 829-39

Chapter Notes

Acknowledgments

The authors would like to thank Linda MacLaren and Karen McElligott for years of service to the Mennonite community affected with CSNB2.

Revision History

- 16 January 2008 (me) Review posted to live Web site
- 9 August 2007 (im) Original submission

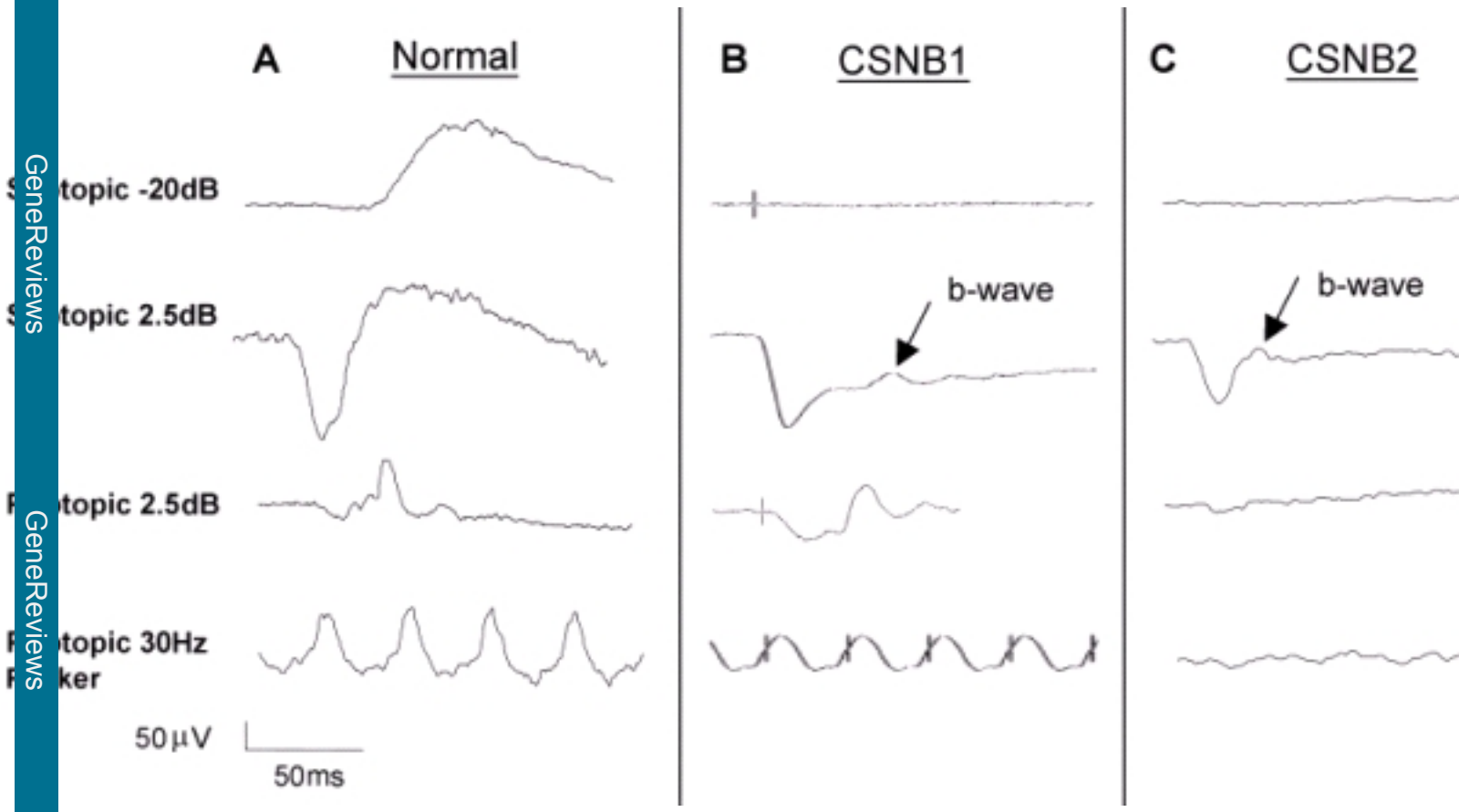

Figure 1. Representative full-field ERGs recorded from three males:
A. Unaffected 35-year-old
B. 66-year-old with CSNB1 (mutation in *NYX*)
C. 35-year-old with CSNB2 (mutation in *CACNA1F*)
Arrows indicate the b-wave, which has lower amplitude than the a-wave (so-called "negative ERG"). Traces in panel C were adapted with the author's permission from Figure 1A of Bech-Hansen et al (2000).