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X-Linked Congenital Stationary Night Blindness

Synonym: X-Linked CSNB

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Summary

Clinical 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. Characteristic ERG findings can help distinguish between complete X-linked CSNB and incomplete X-linked CSNB.

Diagnosis/testing

The diagnosis of X-linked CSNB is established in a male proband with characteristic clinical and electroretinogram (ERG) findings and a family history consistent with X-linked inheritance. Identification of a hemizygous pathogenic variant in *CACNA1F* or *NYX* by molecular genetic testing can confirm the diagnosis if clinical features are inconclusive. The diagnosis of X-linked CSNB may be established in a female proband with ERG findings suggestive of X-linked CSNB and identification of a heterozygous or biallelic pathogenic variant in *CACNA1F* or *NYX* by molecular genetic testing.

Management

Treatment of manifestations: Glasses or contact lenses to treat refractive error (myopia or hyperopia); conventional strabismus surgery may be required to improve binocularity or head posture.

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.

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Genetic counseling

By definition, 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 hemizygous for the pathogenic variant. If the mother of the proband is a carrier, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and will usually not be affected. Males with X-linked CSNB will pass the pathogenic variant to all of their daughters and none of their sons. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible for families in which the pathogenic variant has been identified.

Diagnosis

Suggestive Findings

Males. X-linked congenital stationary night blindness (CSNB) **should be suspected in a male proband** with the following characteristic clinical and electroretinogram (ERG) findings characteristicec of complete X-linked CSNB or incomplete X-linked CSNB (see Table 1):

Characteristic clinical findings:

- Reduced visual acuity
- Night blindness
- Myopia
- Nystagmus (not universal) and strabismus (50%-70%)
- Normal color vision
- Normal fundus examination
- Family history consistent with X-linked inheritance

Characteristic findings on ERG examination:

- 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 the b-wave, not reaching the baseline) [Miyake et al 1986], referred to as the Schubert-Bornschein form [Schubert & Bornschein 1952].
- The ERG can define specific retinal dysfunctions and, in general, differentiate the forms of X-linked CSNB (Table 1), thereby identifying the gene most likely to be involved (see Establishing the Diagnosis).

Table 1. Electroretinogram Findings in Complete and Incomplete X-Linked Congenital Stationary Night Blindness

ERG Finding	Complete (*NYX* X-linked CSNB)	Incomplete (*CACNA1F* X-linked CSNB)
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, sawtooth (square) shaped	Reduced
Photopic b-wave	Slightly reduced	Reduced
Photopic OP	Lost, except for OP4	All OPs are lost.

Table 1. continued from previous page.

ERG Finding	Complete (*NYX* X-linked CSNB)	Incomplete (*CACNA1F* X-linked CSNB)
30-Hz flicker	Normal / slightly reduced	Reduced w/double peak

OP = oscillatory potential

Note: Pupillary responses have been described in the literature and in textbooks as "paradoxic" (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 paradoxic pupillary response. Further clarification of the presence or absence of this phenomenon in individuals with X-linked CSNB may require measurement with pupillometry.

Heterozygous females. X-linked CSNB **should be suspected in a female proband** with the following ERG findings (observed in some heterozygous females):

- Reduced oscillatory potentials (OPs) associated with rod activity [Rigaudière et al 2003]
- Reduced b-wave amplitudes (with unaffected OPs) in one heterozygous female [Rigaudière et al 2003]

Establishing the Diagnosis

Male proband. The diagnosis of X-linked CSNB **is established in a male proband** with the characteristic clinical and ERG findings described in Suggestive Findings and a family history consistent with X-linked inheritance. Identification of a hemizygous pathogenic variant in *CACNA1F* or *NYX* by molecular genetic testing can confirm the diagnosis if clinical features are inconclusive (see Table 2).

Female proband. The diagnosis of X-linked CSNB **may be established in a female proband** with ERG findings suggestive of X-linked CSNB and a heterozygous or biallelic pathogenic variant in *CACNA1F* or *NYX* identified by molecular genetic testing (see Table 2).

Molecular Genetic Testing

Approaches can include **serial single-gene testing** (recommended in individuals with a clear family history consistent with X-linked inheritance) or a **multigene panel** (recommended in individuals without a clear family history consistent with X-linked inheritance).

Serial single-gene testing. For individuals with a clear family history consistent with X-linked inheritance, ERG findings can be used to direct molecular genetic testing to the appropriate gene (see Table 1).

- Sequence analysis of *NYX* should be performed first in individuals with ERG findings consistent with **complete X-linked CSNB** to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- Sequence analysis of *CACNA1F* should be performed first in individuals with ERG findings consistent with **incomplete X-linked CSNB** to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Note: **Targeted analysis** for the *CACNA1F* founder variant c.3167_3168dupC can be performed first in individuals of Dutch-German Mennonite ancestry [Bech-Hansen et al 1998, Boycott et al 2000].

Multigene panel. For individuals without a clear family history consistent with X-linked inheritance, a CSNB multigene panel that includes *CACNA1F*, *NYX*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain

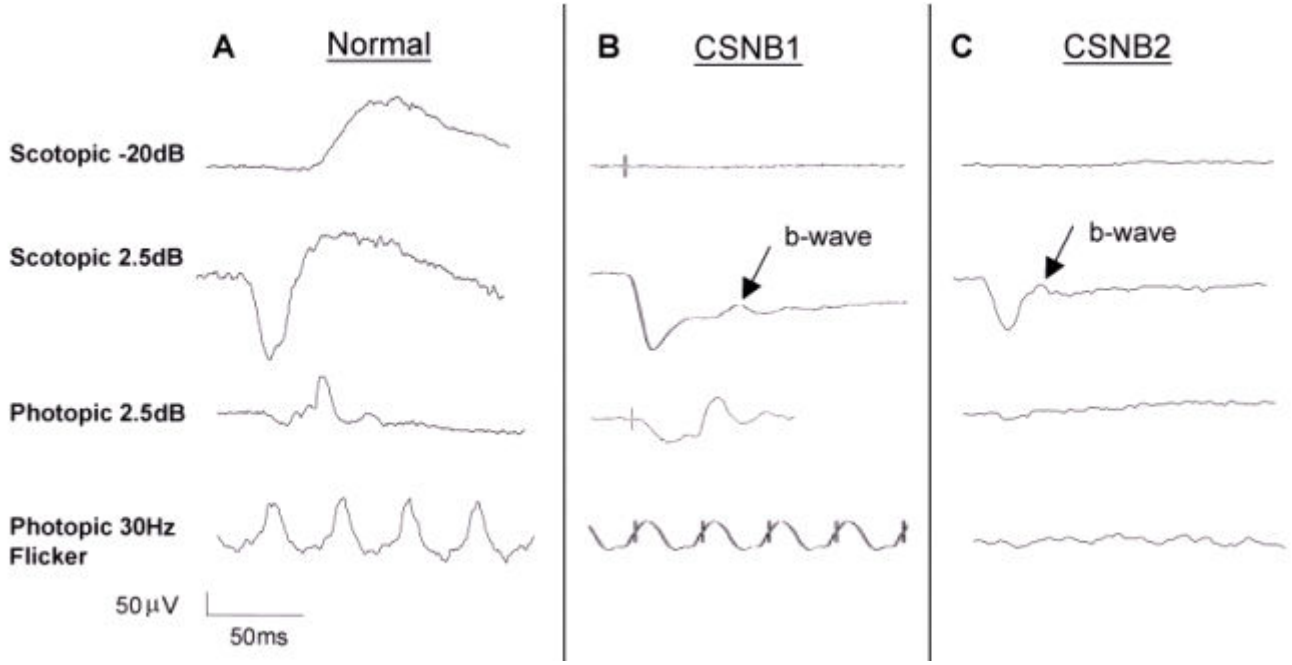

Figure 1. Representative full-field ERGs recorded from three males:

A. Age 35 years, unaffected

B. Age 66 years, with CSNB1A (pathogenic variant in *NYX*)

C. Age 35 years, with CSNB2A (pathogenic variant in *CACNA1F*)

Arrows indicate the b-wave, which has lower amplitude than the a-wave (so-called "negative ERG").

Traces in panel C adapted with the author's permission from Figure 1A of Bech-Hansen et al [2000].

significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 2).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

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

Gene [1, 2]	Proportion of X-Linked CSNB Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
CACNA1F	55% [6, 7]	>98% [6, 7]	5 reported [8]

Table 2. continued from previous page.

Gene [1, 2]	Proportion of X-Linked CSNB Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
NYX	45% [6, 9]	>99% [6, 9, 10]	4 reported [10]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Zeitz [2007]
7. Bijveld et al [2013], Zeitz et al [2015]
8. Bijveld et al [2013], Hauke et al [2013], Zeitz et al [2015], Carss et al [2017]
9. Bech-Hansen et al [2000], Pusch et al [2000]
10. Pusch et al [2000], Bijveld et al [2013]

Clinical Characteristics

Clinical Description

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 that primarily affects males.

Males

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).

Defective dark adaptation. Night blindness is a subjective finding. Individuals with *NYX* X-linked CSNB generally report severe night blindness. Individuals with *CACNA1F* X-linked CSNB do not uniformly report severe night blindness.

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 are reported in 50%-70% of affected individuals [Boycott et al 2000, Allen et al 2003]. Transient head posture with nystagmus was noted in the first two years of life in eight individuals with *CACNA1F* X-linked CSNB and one with *NYX* X-linked CSNB [Simonsz et al 2009].

In a large Mennonite cohort with incomplete (i.e., *CACNA1F*) X-linked CSNB, at least one of the following was **not** present in 72% of individuals: myopia, nystagmus, or night blindness [Boycott et al 2000].

Normal color vision is present in most individuals. Individuals with a severe X-linked CSNB may show mild color vision deficits.

Normal fundus examination is present in most individuals, although those with high myopia may show myopic degeneration.

Females

- In general, heterozygous females do not exhibit clinical signs of X-linked CSNB.
- Females who are homozygous for pathogenic variants in *CACNA1F* with features similar to those in males have been reported [Bech-Hansen et al 1998].

Phenotype Correlations by Gene

NYX pathogenic variants are associated with the complete form of X-linked CSNB (see Table 1) [Bech-Hansen et al 2000, Pusch et al 2000]. Individuals with *NYX* X-linked CSNB generally report severe night blindness.

CACNA1F pathogenic variants are associated with the incomplete form of X-linked CSNB [Bech-Hansen et al 1998, Strom et al 1998] (see Table 1). Individuals with *CACNA1F* X-linked CSNB do not uniformly report severe night blindness.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

Penetrance

Penetrance of X-linked CSNB is probably 100%, but expressivity is variable [Boycott et al 2000]; individuals with mild presentations may be missed if electroretinography is not performed.

Nomenclature

X-linked CSNB has in the past been referred to as Schubert-Bornschein CSNB, which is a reference to the characteristic "negative" waveform (a-wave larger than the b-wave in response to a bright flash in the scotopic state) 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 ***CACNA1F*** founder variant, c.3166dupC (alias: c.3167_3168dupC), has been reported in individuals of Dutch-German Mennonite descent [Bech-Hansen et al 1998, Boycott et al 1998, Boycott et al 2000].

A common pathogenic variant in ***NYX***, c.856delG, has been identified in Flemish individuals from Belgium [Leroy et al 2009].

A common founder variant in ***NYX***, c.85_108del, has been identified in the United States [Bech-Hansen et al 2000].

Genetically Related (Allelic) Disorders

NYX. One other phenotype may be associated with mutation of *NYX*. High myopia in two unrelated males was associated with two novel pathogenic missense variants in *NYX*, suggesting that pathogenic variants 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. Retinal and optic atrophy, associated with progressive visual decline, has been described in two Japanese brothers [Nakamura et al 2003].

Other phenotypes associated with germline pathogenic variants in *CACNA1F* are summarized in Table 3. Disorders included in Table 3 have overlapping phenotypic features with X-linked congenital stationary night blindness and should be considered in the differential diagnosis.

Table 3. Other *CACNA1F*-Related Disorders to Consider in the Differential Diagnosis of X-Linked Congenital Stationary Night Blindness

CACNA1F-Related (Allelic) Disorder	Clinical Features of Allelic Disorder	
	Overlapping w/X-linked CSNB	Distinguishing from X-linked CSNB
Åland Island eye disease (AIED; Forsius-Eriksson syndrome) [1] (OMIM 300600)	• Significant phenotypic overlap between AIED & CSNB2A • Retinal disorder • ↓ visual acuity • Nystagmus • Astigmatism • Defective dark adaptation • ERG reveals abnormalities in both photopic & scotopic functions.	• Fundus hypopigmentation • Myopia is progressive. • Protan color vision defect
X-linked cone-rod dystrophy (CORDX3) [2] (OMIM 300476)	• Several features of CSNB2A • Modest progressive dysfunction of photoreceptors	Variable features incl: • Constricted visual fields • Central scotomas • General ↓ of sensitivity in central field • Red/green or red color defects
X-linked retinal disorder [3]	Clinical & ERG similarities to CSNB2A	• Intellectual disability • Manifestations in heterozygous female (attributed to unique gain-of-function missense variant in *CACNA1F*) [4]

CSNB = congenital stationary night blindness; CSNB2A = CSNB caused by a pathogenic variant in *CACNA1F*; ERG = electroretinogram

1. A novel pathogenic variant in *CACNA1F* has been identified in affected individuals from the original family with AIED [Jalkanen et al 2007].

2. A pathogenic variant in *CACNA1F* has been identified in one Finnish family [Jalkanen et al 2006].

3. Described in a large Maori family [Hope et al 2005]

4. Hemara-Wahanui et al [2005]

Differential Diagnosis

Only a few conditions may initially be confused with the X-linked form of congenital stationary night blindness (CSNB).

Table 4. Disorders to Consider in the Differential Diagnosis of X-Linked Congenital Stationary Night Blindness

Fundus [1]	DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
				Overlapping w/X-linked CSNB	Distinguishing from X-linked CSNB
Normal fundus	CSNB (non-X-linked)	See footnote 2.	AR AD	Most autosomal CSNB is clinically identical, w/ exception of AD CSNB, Nougaret type.	• Family history consistent w/XL inheritance may differentiate XL forms of CSNB from AD & AR forms. • In AD CSNB, Nougaret type (OMIM 610444) there is no significant refractive error & ERG

Table 4. continued from previous page.

Fundus [1]	DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
				Overlapping w/X-linked CSNB	Distinguishing from X-linked CSNB
					waveform is Riggs type (not Schubert-Bornshein) [3] w/ minimal a-wave in response to scotopic bright flash.
	Blue cone monochromacy (OMIM 303700)	*OPN1LW* *OPN1MW*	XL	• Poor vision • Nystagmus	• Abnormal color vision • Almost completely abolished photopic ERG contrasting w/ normal or minimally affected scotopic ERG • Fundus exam in young males is normal; some males develop macular atrophy in late adulthood.
	FRMD7-related infantile nystagmus	*FRMD7*	XL	• Poor vision • Nystagmus	• Normal ERG • Normal VEP • Normal foveal contour
Abnormal fundus	Ocular albinism type I (OMIM 300500)	*OA1*	XL	• Poor vision • Nystagmus	• Iris transillumination • Foveal hypoplasia • Heterozygous females have fundus signs (hypopigmentation of retinal pigment epithelium). [4] • Absence of selective ↓ in amplitude of b-wave on ERG • VEP responses show propensity for more crossing fibers than expected at level of chiasm.
	X-linked juvenile retinoschisis	*RS1*	XL	• Visual acuity ↓ to same range as in XL CSNB • Selective ↓ in amplitude of b-wave on ERG	Fundus exam shows foveal schisis or foveal findings in virtually all affected males & ~50% have areas of peripheral retinoschisis.
	Oguchi disease [5] (OMIM 258100, 613411)	*SAG* *GRK1*	AR	Non-progressive	Fundus has abnormal color that becomes normal w/prolonged dark adaptation (Mizuo phenomenon). [6]

Table 4. continued from previous page.

Fundus [1]	DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
				Overlapping w/X-linked CSNB	Distinguishing from X-linked CSNB
	Fundus albipunctatus [7] (OMIM 136880)	*RDH5* *RLBP1*	AR AD	Non-progressive	• Fundus shows discretely scattered white retinal dots. • ERG, when recorded under standard conditions, shows selective ↓ in b-wave that normalizes w/prolonged dark adaptation. [6]

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; ERG = electroretinogram; MOI = mode of inheritance; VEP = visual evoked potential; XL = X-linked

1. X-linked CSNB is characterized by a normal fundus.

2. See Night blindness, congenital stationary: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

3. Riggs [1954]

4. Charles et al [1993]

5. Oguchi disease is a form of CSNB reported in the Japanese.

6. Dryja [2000]

7. Fundus albipunctatus is a form of CSNB.

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 (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Ophthalmologic examination
- Electroretinography
- Dark adaptation (optional)
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

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

Occasionally, 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.

Evaluation of Relatives at Risk

For infants identified with high myopia, unusual head posture, or nystagmus and a family history of CSNB, ophthalmic examination and molecular genetic testing may confirm the diagnosis of CSNB, obviating the need for neuroimaging or clinical electrophysiologic testing under sedation or general anesthesia.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

By definition, 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 hemizygous for the *CACNA1F* or *NYX* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected male, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *CACNA1F* or *NYX* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo CACNA1F* or *NYX* pathogenic variant, in which case the mother is not a carrier.
- If the proband is female and has biallelic pathogenic variants (rare), both the mother and the father may have X-linked CSNB-causing pathogenic variants (i.e., the mother may be a carrier and the father may be affected) [Bech-Hansen et al 1998].

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *CACNA1F* or *NYX* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the variant will be heterozygous and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *CACNA1F* or *NYX* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the X-linked CSNB-causing pathogenic variant to:

- All of their daughters, who will be heterozygous and will usually not be affected;

- None of their sons.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the pathogenic variant, and the aunts' offspring, depending on their sex, may be at risk of being carriers or of being affected.

Carrier (Heterozygote) Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous (carriers) for this X-linked disorder will usually not be affected. (2) Identification of female heterozygotes requires either (a) prior identification of the *CACNA1F* or *NYX* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing 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, are carriers, or are at increased risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *CACNA1F* or *NYX* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for X-linked CSNB are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Fighting Blindness Canada**
  890 Yonge Street
  12th Floor

Toronto Ontario M4W 3P4
Canada
Phone: 800-461-3331 (toll-free); 416-360-4200
Fax: 416-360-0060
Email: info@fightingblindness.ca
www.fightingblindness.ca

- **Foundation Fighting Blindness**
  7168 Columbia Gateway Drive
  Suite 100
  Columbia MD 21046
  Phone: 800-683-5555 (toll-free); 800-683-5551 (toll-free TDD); 410-423-0600
  Email: info@fightblindness.org
  www.fightingblindness.org
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **eyeGENE – National Ophthalmic Disease Genotyping Network Registry**
  Phone: 301-435-3032
  Email: eyeGENEinfo@nei.nih.gov
  https://eyegene.nih.gov/

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Congenital Stationary Night Blindness: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CACNA1F	Xp11.23	Voltage-dependent L-type calcium channel subunit alpha-1F	CACNA1F @ LOVD	CACNA1F	CACNA1F
NYX	Xp11.4	Nyctalopin	NYX@LOVD	NYX	NYX

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Congenital Stationary Night Blindness (View All in OMIM)

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

Molecular 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. Pathogenic variants identified in these genes impinge on synaptic transmission from photoreceptors (rods and cones) to inner retinal cells.

Pathogenic variants in *NYX* are predicted to cause 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].

Expression studies have shown that some (not all) *CACNA1F* pathogenic missense variants 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 variants may affect the assembly or expression of the presynaptic ribbon complex [Hoda et al 2006]. Pathogenic nonsense and frameshift variants are predicted to cause loss of channel function or/and photoreceptor synapses.

Mechanism of disease causation. Loss of function

Table 5. X-Linked Congenital Stationary Night Blindness: Notable Pathogenic Variants by Gene

Gene	Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
CACNA1F	NM_005183.2	c.3166dupC (c.3167_3168dupC)	p.Leu1056ProfsTer11 (Leu991insC)	Founder variant reported in persons of Dutch-German Mennonite descent [Boycott et al 2000]
NYX	NM_022567.2 NP_072089.1	c.85_108del	p.Arg_Ala36del	Founder variant identified in the US [Bech-Hansen et al 2000]
		c.856delG	p.Asp286ThrfsTer62	Identified in Flemish persons from Belgium [Leroy et al 2009]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

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Chapter Notes

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