

Congenital Stationary Night Blindness Panel

DISORDER ALSO KNOWN AS

Congenital Stationary Night Blindness with Myopia, Hemeralopia-Myopia, Myopia-Night Blindness, Nyctalopia

PANEL GENE LIST

CABP4, CACNA1F, CHM, GNAT1, GRM6, NYX, PDE6B, RDH5, RHO, RPE65, SAG, and TRPM1

CLINICAL FEATURES

Congenital stationary night blindness (CSNB) is a genetically heterogeneous group of largely non-progressive retinal dystrophies. The condition primarily affects rod photoreceptors of the retina, impairing night vision. However, under adequate lighting, there is often no visual deficit. Moderate to high myopia, nystagmus and/or strabismus may also occur. Patients are generally diagnosed by electroretinography (ERG). Individuals with stationary night blindness have an abnormal dark-adaptation rod-mediated b-wave response on ERG.^{2,3} Reduced oscillatory potentials and cone ERGs that are normal to mildly abnormal are also typical findings.^{2,3}

CSNB can be categorized into two different types, the Schubert-Bornschein type and the Riggs type. Schubert-Bornschein type CSNB presents as decreased visual acuity, myopia, and nystagmus. Riggs type CSNB presents as normal visual acuity with no symptoms of myopia or nystagmus.¹⁷ Differences in the electroretinogram findings exist as well. The Schubert-Bornschein type CSNB is characterized by a smaller amplitude of the b-wave than the a-wave, whereas the Riggs type has a proportionate reduction of both waves.¹⁷

The Schubert-Bornschein type of CSNB can be further categorized into two subgroups, “complete” or “incomplete,” defined by the presence or the absence of residual rod function measured by dark adaptometry or electroretinogram (ERG). Complete CSNB involves ON bipolar cell dysfunction, and incomplete involves both ON and OFF bipolar cell dysfunction.^{17,22} The variants in the NYX and TRPM1 genes are mainly responsible for the complete form of CSNB. The GRM6 gene is another cause of complete CSNB.³² Variants in the genes CABP4 and CACNA1F are associated with incomplete CSNB.¹⁷

Forms of CSNB with abnormal fundus appearance can be separated into two disorders, fundus albipunctatus (FA) and Oguchi disease, both inherited in an autosomal recessive manner. Fundus albipunctatus is characterized by white dots on the fundus except in the macular region.³¹ Fundus albipunctatus (FA) is a retinal disorder characterized by night blindness and delayed dark adaptation after exposure to bright light. FA may occur with or without cone dystrophy, but individuals that experience FA with cone dystrophy are generally 40 years or older.^{11,12} Oguchi disease is characterized by a golden or gray-white discoloration of the fundus which is absent in the dark-adapted state and reappears after the onset of light. The course of dark adaptation is extremely retarded in rods but normal in cone photoreceptors.⁷

The CSNB panel may clarify a clinical diagnosis or identify a genetic diagnosis for CSNB or a CSNB-related disorder. If a genetic diagnosis is found, genetic testing and recurrence risk information would be available for at-risk family members. In addition, having an identified genetic diagnosis may or may not impact medical management or treatment of the condition.

GENETICS

Autosomal dominant, autosomal recessive or x-linked recessive.

TEST METHODS

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

TEST SENSITIVITY

Autosomal Dominant

GNAT1 gene: Variants in the GNAT1 gene are rare, but have been reported in association with both adCSNB¹⁶ and arCSNB.¹⁷

PDE6B gene: Variants in the PDE6B gene are rare, as they have only been reported a small number of families with CSNB.^{20,21}

RHO gene: RHO variants have been reported in a small number of individuals with CSNB.^{14,15}

Autosomal Recessive

CABP4 gene: Variants in the CABP4 gene were identified in 2 out of 35 families (~6%) with incomplete CSNB or uncertain CSNB type.¹⁸

GRM6 gene: Variants in the GRM6 gene were identified in 3 out of 26 (~11%) unrelated patients diagnosed with complete CSNB.³¹ Variants were also identified in 3 out of 5 families diagnosed with autosomal recessive complete CSNB, two of whom were previously negative for NYX and CACNA1F.¹⁹

RDH5 gene: In a number of small familial studies, the identification of RDH5 variants in affected individuals with FA has ranged from 75% to 100%.^{11,12}

RPE65 gene: RPE65 gene variants have been reported in individuals with Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP). Variants make up about 6-16% of LCA and approximately 2% of autosomal recessive RP.^{29,30}

SAG gene: Most Japanese patients diagnosed with Oguchi disease were homozygous or compound heterozygous for variants in the SAG gene.^{7,9} The common c.926delA variant has been reported in approximately 2.5% of Japanese patients diagnosed with autosomal recessive retinitis pigmentosa,⁸ and in 80% of the Japanese patients diagnosed with Oguchi's disease.⁷

TRPM1 gene: Variants in the TRPM1 gene have been identified in approximately 22-26% of the affected patients with complete CSNB who tested negative for variants in the NYX and GRM6 genes.^{4,5} In another study, variants in the TRPM1 gene were identified in 6 out of 8 (75%) proband females who tested negative for variants in NYX and GRM6.⁶ In two studies, a single variant was identified in approximately 16-20% of patients with CSNB.^{5,6}

X-linked recessive

CACNA1F gene: Variants in the CACNA1F gene were identified in 30 of 33 families (~91%) diagnosed with incomplete X-linked CSNB. ¹⁰ A deletion of exon 30 of the CACNA1F is the variant responsible for Aland Island Eye Disease (AIED) also known as Forsius-Eriksson syndrome. ¹³

NYX gene: Variants in the NYX gene have been identified in all males affected with the complete form of X-linked CSNB. ^{1,2,3}

X-linked dominant

CHM gene: The CHM gene is the only known gene to cause choroideremia, an x-linked retinal dystrophy characterized by night blindness and decreased visual activity. ²⁸

Gene Protein Inheritance Disease Associations	Gene Protein Inheritance Disease Associations	Gene Protein Inheritance Disease Associations	Gene Protein Inheritance Disease Associations
CABP4	Calcium binding protein 4	AR	CSNB (incomplete); cone-rod synaptic disorder, congenital non-progressive
CACNA1F	Calcium channel voltage-dependent alpha-1F subunit	XLR	CSNB (incomplete); cone-rod dystrophy; Aland Island eye disease
CHM	Rab escort protein 1	XLD	Choroideremia
GNAT1	Guanine nucleotide-binding protein alpha-transducing activity polypeptide 1	AD	CSNB (Riggs)
GRM6	Glutamate receptor, metabotropic, 6	AR	CSNB (complete)
NYX	Nyctalopin	XLR	CSNB (complete)
PDE6B	PDE6B Phosphodiesterase 6B cGMPspecific, rod, beta	AD	CSNB (Riggs); retinitis pigmentosa
RDH5	Retinol dehydrogenase 5	AR	Fundus albipunctatus
RHO	Rhodopsin	AD	CSNB (Riggs); retinitis pigmentosa; retinitis punctate albescens
RPE65	Retinal pigment epithelium-specific protein	AR	Leber congenital amaurosis and retinitis pigmentosa
SAG	S-antigen	AR	Oguchi disease; retinitis pigmentosa
TRPM1	Transient receptor potential cation channel, subfamily M, member 1	AR	CSNB (complete)

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