

Congenital Stationary Night Blindness Panel

Congenital stationary night blindness also known as: Congenital Stationary Night Blindness with Myopia, Hemeralopia-Myopia, Myopia-Night Blindness, Nyctalopia

Panel Gene List: CABP4, CACNA1F, GNAT1, GRM6, NYX, RDH5, RHO, SAG and TRPM1

Clinical Features:

Congenital stationary night blindness (CSNB) is a group of congenital retinal dystrophies currently associated with two X-linked genes (NYX, CACNA1F), ten autosomal recessive genes (CABP4, GNB3, GPR179, GRK1, GRM6, LRIT3, RDH5, SAG, SLC24A1 and TRPM1)^{18,24}, and three autosomal dominant genes (GNAT1, PDE6B, RHO). CSNB can be subcategorized into two subgroups, “complete” or “incomplete,” defined by the presence or the absence of residual rod function measured by dark adaptometry or electroretinogram (ERG). The NYX and the TRPM1 gene variants are mainly responsible for the complete form of CSNB.

Patients with complete X-linked CSNB usually have high myopia with a tigroid-appearing fundus. Some patients have mild nystagmus. All patients with stationary night blindness have an abnormal dark-adaptation curve and an abnormal ERG. The ERG demonstrates a severely reduced or absent dark-adapted rod-mediated b-wave response^{3,15}. In particular, this analysis will produce a subnormal ratio of b-wave to a-wave amplitude when using a white flash in the dark^{3,15}. Reduced oscillatory potentials and cone ERGs that are normal to mildly abnormal are also typical findings^{3,15}.

CSNB with abnormal fundus appearance can be separated into two disorders, Fundus albipunctatus (FA) and Oguchi disease which are inherited in an autosomal recessive manner. Fundus albipunctatus is characterized by white dots on the fundus except in the macular region²⁴. The typical clinical presentation of Oguchi disease is 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 photoreceptors⁷.

Inheritance Pattern/Genetics:

Autosomal dominant, autosomal recessive or x-linked recessive

Test Methods:

The coding regions and splice junctions of the 9 genes of this panel are enriched using a proprietary targeted capture system developed by GeneDx. The targeted regions are

sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequence is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 19 reads are achieved by NextGen sequencing.

Test Sensitivity:

Autosomal Dominant

GNAT1 gene: Guanine nucleotide binding protein, alpha transducing activity polypeptide 1
Rarely, variants in the GNAT1 gene have been reported in association with adCSNB^{5,16} and arCSNB¹⁰.

RHO gene: Rhodopsin

RHO variants have been reported in a few cases of CSNB^{1,4}.

Autosomal Recessive

CABP4 gene: Calcium-binding protein 4

Variants in the CABP4 gene were identified in 2 out of 35 families (~6%) with incomplete CSNB or uncertain CSNB type²³.

GRM6 gene: Glutamate receptor, metabotropic, 6

Variants in the GRM6 gene were identified in 3 out of 26 (~11%) unrelated patients diagnosed with complete CSNB⁶. Variants were also identified in 3 out of 5 families diagnosed with autosomal recessive complete CSNB²². Two male patients in the latter study were previously determined to be negative for variants in the NYX and CACNA1F genes.

RDH5 gene: Retinol Dehydrogenase 5

The RDH5 gene is associated with fundus albipunctatus (FA), which is a retinal disorder characterized by night blindness and delayed dark adaptation after exposure to bright light. 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, 21}.

SAG gene: S-antigen; retina and pineal gland (arrestin)

Most Japanese patients diagnosed with Oguchi disease were homozygous or compound heterozygous for variants in the SAG gene^{7,13}. The common c.926delA variant has been reported in approximately 2.5% of Japanese patients diagnosed with autosomal recessive retinitis pigmentosa¹⁴, and in 80% of the Japanese patients diagnosed with Oguchi's disease⁷.

TRPM1 gene: Transient receptor potential cation channel, subfamily M, member 1

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^{2,9}. 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 GRM6¹⁷. In two studies, only a single variant was identified in approximately 16-20% of patients^{2,17}.

X-linked recessive

CACNA1F gene: Calcium channel, voltage-dependent, alpha-1F subunit

Variants in the CACNA1F gene were identified in 31 of 34 families (~91%) diagnosed with incomplete X-linked CSNB¹⁹. A deletion of exon 30 of the CACNA1F is the variant responsible for Aland Island Eye Disease (AIED) also known as Forsius-Eriksson syndrome⁸.

NYX gene: nyctalopin

Variants in the NYX gene have been identified in all males affected with the complete form of X-linked CSNB^{3,15,20}.

Gene	Protein	Inheritance	Disease Associations
<i>CABP4</i>	Calcium-binding protein 4	AR	Cone-rod synaptic disorder, congenital non-progressive
<i>CACNA1F</i>	Calcium channel, voltage-dependent, alpha-1F subunit	XLR	Night blindness, congenital stationary (incomplete), 2A; Aland Island eye disease; cone-rod dystrophy, 3
<i>GNAT1</i>	Guanine nucleotide binding protein, alpha transducing activity polypeptide 1	AD	Night blindness, congenital stationary, 3; ?Night blindness, congenital stationary, type 1G
<i>GRM6</i>	Glutamate receptor, metabotropic, 6	AR	Night blindness, congenital stationary (complete), 1B
<i>NYX</i>	nyctalopin	XLR	Night blindness, congenital stationary (complete), 1A
<i>RDH5</i>	Retinol Dehydrogenase 5	AR	Fundus albipunctatus
<i>RHO</i>	Rhodopsin	AD	Night blindness, congenital stationary, autosomal dominant 1; Retinitis pigmentosa 4; Retinitis punctata albescens
<i>SAG</i>	S-antigen; retina and pineal gland (arrestin)	AR	Oguchi disease-1; Retinitis pigmentosa 47
<i>TRPM1</i>	Transient receptor potential cation channel, subfamily M, member 1	AR	Night blindness, congenital stationary (complete), 1C

References:

1. al-Jandal et al., (1999) Human Variant 13:75-81 (PMID: 9888392)
2. Audo et al., (2009) Am J Hum Genet 85: 720-729 (PMID: 19896113)
3. Bech-Hansen et al., (2000) Nat Genet 26: 319-323 (PMID: 11062471)
4. Dryja et al., (1993) Nat Genet 4:280-283 (PMID: 8358437)
5. Dryja et al., (1996) Nat Genet 13:358-360 (PMID: 8673138)
6. Dryja et al., (2005) Proc Natl Acad Sci U.S.A. 102:4884-9 (PMID: 15781871)
7. Fuchs et al., (1995) Nat Genet 10:360-362 (PMID: 7670478)
8. Jalkanen et al., (2007) Invest Ophthalmol Vis Sci 48:2498-502 (PMID: 17525176)
9. Li et al., (2009) Am J Hum Genet 85:711-719 (PMID: 19878917)
10. Naeem et al., (2012) Invest Ophthalmol Vis Sci 53(3):1353-61 (PMID: 22190596)

11. Nakamura et al., (2000) Invest Ophthalmol Vis Sci 41(12):3925-32 (PMID: 11053295)
12. Nakamura et al., (2003) Doc Ophthalmol 107(1):3-11 (PMID: 12906118)
13. Nakamura et al., (2004) Ophthalmology 111(7):1410-1414 (PMID: 15234147)
14. Nakazawa et al., (1998) Arch Ophthalmol 116:498-501 (PMID: 9565049)
15. Pusch et al., (2000) Nat Genet 26:324-327 (PMID: 11062472)
16. Szabo V et al., (2007) Hum Mutat 28(7):741-2 (PMID: 17584859)
17. van Genderen et al., (2009) Am J Hum Genet 85: 730-736 (PMID: 19896109)
18. Vincent et al., (2016) Am J Hum Genet 98: 1011-1019 (PMID: 27063057)
19. Wutz et al., (2002) Eur J Hum Genet 10:449-56 (PMID: 12111638)
20. Xiao et al., (2006) J Hum Genet 51:634-640 (PMID: 16670814)
21. Yamamoto H et al., (1999) Nat Genet 22:188-91 (PMID: 10369264)
22. Zeitz et al., (2005) Invest Ophthalmol Vis Sci 46(11):4328-35 (PMID: 16249515)
23. Zeitz et al., (2006) Am J Hum Genet 79(4):657-67 (PMID: 16960802)
24. Zeitz et al., (2014) Prog Retin Eye Res 45:58-110 (PMID: 25307992)