

X-Linked Congenital Stationary Night Blindness (CACNA1F)

Disorder also known as: Congenital Stationary Night Blindness with Myopia, Hemeralopia-Myopia, Myopia-Night Blindness, Nyctalopia

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:

X-linked recessive

Test Sensitivity:

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.

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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.

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)