Cone-rod Synaptic Disorder (CABP4)

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 region[24]. 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 photoreceptors[7].

Inheritance Pattern:
Autosomal recessive

Test Sensitivity:
Variants in the CABP4 gene were identified in 2 out of 35 families (~6%) with incomplete CSNB or uncertain CSNB type[23].

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 Opthalmol 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)