

## TRPM1 Gene Analysis in Congenital Stationary Night Blindness

### 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.<sup>2,3</sup> Reduced oscillatory potentials and cone ERGs that are normal to mildly abnormal are also typical findings.<sup>2,3</sup>

CSNB can be 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.<sup>1,8</sup> The variants in the NYX and TRPM1 genes are primarily responsible for the complete form of CSNB, while variants in the CABP4 and CACNA1F genes are associated with incomplete CSNB.<sup>1</sup>

Causative variants in the TRPM1 gene are associated with CSNB type 1C, which is characterized by the absence of residual rod function (complete CSNB1C). Additional features include early high myopia, nystagmus, and strabismus.<sup>7</sup>

This test may clarify a clinical diagnosis or identify a genetic diagnosis for TRMP1-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.

### Inheritance Pattern/Genetics:

Autosomal recessive

### 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 is analyzed for sequence variants. Concurrent deletion/duplication testing is performed 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. If present, apparently homozygous sequence variants are confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. 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.

### **Test Sensitivity:**

Variants in the TRPM1 gene have been identified in approximately 22-26% of affected patients with complete CSNB who tested negative for variants in the NYX and GRM6 genes.<sup>4,5</sup> 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.<sup>6</sup>

### **References:**

1. Naeem et al. (2012) *Investigative Ophthalmology & Visual Science* 53 (3):1353-61 (PMID: 22190596)
2. Bech-Hansen et al. (2000) *Nature Genetics* 26 (3):319-23 (PMID: 11062471)
3. Pusch et al. (2000) *Nature Genetics* 26 (3):324-7 (PMID: 11062472)
4. Li et al. (2009) *Am. J. Hum. Genet.* 85 (5):711-9 (PMID: 19878917)
5. Audo et al. (2009) *Am. J. Hum. Genet.* 85 (5):720-9 (PMID: 19896113)
6. van et al. (2009) *American Journal Of Human Genetics* 85 (5):730-6 (PMID: 19896109)
7. Miraldi Utz et al. (2018) *JAMA Ophthalmol* 136 (4):389-398 (PMID: 29522070)
8. Vincent et al. (2016) *Am. J. Hum. Genet.* 98 (5):1011-9 (PMID: 27063057)