CACNA1F, CABP4, GNAT1, GRM6, NYX, PDE6B, RDH5, RHO, SAG, and TRPM1
Gene Analysis in Congenital Stationary Night Blindness

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

Mendelian Inheritance in Man Number:

<table>
<thead>
<tr>
<th>Gene</th>
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Clinical features:
Congenital stationary night blindness (CSNB) is a group of congenital retinal dystrophies currently associated with two X-linked genes (NYX, CACNA1F), six autosomal recessive genes (CABP4, GRK1, GRM6, RDH5, SAG, TRPM1), 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 mutations 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 (Pusch et al., 2000 and Bech-Hansen et al., 2000). In particular, this analysis will produce a subnormal ratio of b-wave to a-wave amplitude when using a white flash in the dark (Pusch et al., 2000 and Bech-Hansen et al., 2000). Reduced oscillatory potentials and cone ERGs that are normal to mildly abnormal are also typical findings (Pusch et al., 2000 and Bech-Hansen et al., 2000).

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. (Fuchs et al., 1995)

Differential diagnosis of congenital night blindness
CSNB, Leber congenital amaurosis (LCA), and complete achromatopsia are three types of congenital retinal dystrophies that overlap clinically, as all patients present in early childhood with visual impairment and nystagmus.

Inheritance pattern:
CACNA1F and NYX: X-linked recessive
CABP4, GNAT1, GRM6, RDH5, SAG and TRPM1: Autosomal recessive
GNAT1, PDE6B, and RHO: Autosomal dominant
Reasons for referral:
1. Confirmation of a clinical diagnosis.
2. Development of an appropriate management plan.
3. Genetic counseling.
4. Prenatal diagnosis in families with a defined mutation.

Test method:
X-linked CSNB: CACNA1F and NYX genes
DNA sequence is obtained and analyzed for the coding sequence and splice site junctions of the NYX gene (exons 1-2) and CACNA1F (exons 1-48) genes. In females, where sequencing cannot detect large deletions, targeted array CGH analysis with exon-level resolution (ExonArrayDx) can be performed to evaluate for a deletion or duplication of one or more exons of the NYX gene. ExonArrayDx is not yet available for the CACNA1F gene.

Autosomal recessive CSNB: CABP4, GRM6, TRPM1, SAG, GNAT1 and RDH5 genes
DNA sequence is obtained and analyzed for the coding sequence and splice site junctions of the CABP4 (exons 1-6), GRM6 (exons 2-16), TRPM1 (exons 2-27), and RDH5 (exons 2-5) genes. Sequence analysis of the SAG gene is offered as two tiers. Tier 1 includes sequence analysis of exon 11 for the common c.926delA mutation (reported by Fuchs et al, 1995 as 1147delA). Tier 2 includes sequence analysis of the remaining exons (exons 2-10, 12-16). If sequencing identifies a mutation on only one allele of the SAG, TRPM1, or RDH5 gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of the CABP4, GRM6, TRPM1, and RDH5 genes. ExonArrayDx is not yet available for the SAG gene.

Autosomal dominant CSNB: GNAT1, PDE6B, and RHO genes
DNA sequence is obtained and analyzed for the coding sequence and splice site junctions of the RHO (exons 1-5) and GNAT1 (exons 1-9) genes. The PDE6B gene sequence analysis is only offered as part of the autosomal recessive retinitis pigmentosa 7 genes panel only.

Test sensitivity:
CACNA1F gene: Calcium channel, voltage-dependent, alpha-1F subunit
Mutations in the CACNA1F gene were identified in 31 of 34 families (~91%) diagnosed with incomplete X-linked CSNB (Wutz, 2002). A deletion of exon 30 of the CACNA1F is the mutation responsible for Aland Island Eye Disease (AIED) also known as Forsius-Eriksson syndrome (Jalkanen, 2007).

NYX gene: nyctalopin
Mutations in the NYX gene have been identified in all males affected with the complete form of X-linked CSNB (Pusch et al., 2000, Bech-Hansen et al., 2000, and Xiao et al., 2006). In females, full gene sequencing analysis along with targeted array CGH analysis with exon-level resolution (ExonArrayDx) is expected to provide a sensitivity comparable to that in males.

CABP4 gene: Calcium-binding protein 4
Mutations in the CABP4 gene were identified in 2 out of 35 families (~6%) with incomplete CSNB or uncertain CSNB type (Zeitz, 2006).

GRM6 gene: Glutamate receptor, metabotropic, 6
Mutations in the GRM6 gene were identified in 3 out of 26 (~11%) unrelated patients diagnosed with complete CSNB (Dryja, 2005). Mutations were also identified in 3 out of 5 families diagnosed with autosomal recessive complete CSNB (Zeitz, 2005). Two male patients in the latter study were previously determined to be negative for mutations in the NYX and CACNA1F genes.

TRPM1 gene: Transient receptor potential cation channel, subfamily M, member 1
Mutations in the TRPM1 gene have been identified in approximately 22-26% of the affected patients with complete CSNB who tested negative for mutations in the NYX and GRM6 genes (Li et al., 2009 and Audo et al., 2009). In another study, mutations in the TRPM1 gene were identified in 6 out of 8 (75%) proband females who tested negative for mutations in NYX and GRM6 (Van Genderen et al., 2009). In two studies, only a single mutation was identified in approximately 16-20% of patients (Van Genderen et al., 2009; Audo et al., 2009).

SAG gene: S-antigen; retina and pineal gland (arrestin)
Most Japanese patients diagnosed with Oguchi disease were homozygous or compound heterozygous for mutations in the SAG gene (Fuchs et al., 1995; Nakamura et al., 2004). The common c. 926delA mutation has been reported in approximately 2.5% of Japanese patients diagnosed with autosomal recessive retinitis pigmentosa (Nakazawa et al., 1998), and in 80% of the Japanese patients diagnosed with Oguchi’s disease (Fuchs et al., 1995).
GNAT1 gene: Guanine nucleotide binding protein, alpha transducing activity polypeptide 1
Rarely, mutations in the GNAT1 gene have been reported in association with adCSNB (Dryja, 2006; Szabo V, 2007) and arCSNB (Naeem, 2012)

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 mutations in affected individuals with FA has ranged from 75% to 100% (Yamamoto, 1999; Nakamura, 2000; Nakamura, 2003).

RHO gene: Rhodopsin
RHO mutations have been reported in a few cases of CSNB (Dryja, 1993; al-Jandal, 1999).

PDE6B gene: Phosphodiesterase 6B, cGMP-specific, rod beta subunit
Only one mutation in PDE6B has been reported in a large Danish family in association with adCSNB

Mutation spectrum:
CACNA1F, NYX, and TRPM1 genes: Missense, nonsense, frameshifts, and gross deletions have been reported.
CABP4 gene: Only frameshift and nonsense mutations have been demonstrated to be disease-causing in this gene (Fuchs et al., 1995; Nakamura et al., 2004; Nakazawa et al., 1998). While missense variants have also been reported in the literature, none have been shown to segregate with disease.
SAG gene: Only nonsense and frameshift mutations have been reported in association with Oguchi disease.
RDH5 gene: The vast majority of mutations observed in the RDH5 gene are missense mutations; however, frameshift mutations have also been observed.
GNAT1 gene: Only missense mutations have been reported.
GRM6 gene: Missense, nonsense, and frameshifts, mutation have been reported.
RHO gene: The vast majority of mutations are missense changes that usually have a gain-of-function effect.
PDE6B gene: Only a single missense mutation has been reported in this gene in association with adCSNB

Specimen Requirements and Shipping/Handling:

- **Blood**: A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes**: Can be used as an alternative to blood for NYX and TRPM1 sequencing only. Gene deletion/duplication testing (ExonArrayDx) requires submission of a venous blood sample. When sending a buccal sample, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children less than 6 months of age.
- **Prenatal Diagnosis**: For prenatal testing for a known mutation in the CACNA1F, CABP4, GNAT1, GRM6, NYX, PDE6B, RDH5, RHO, SAG, or RPM1 genes, please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

Required Forms:

- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Congenital Stationary Night Blindness” page on our website: www.genedx.com

References Cited: