NYX, TRPM1, SAG, RDH5, and RHO 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: 300278 (NYX), 310500 (X-linked Congenital Stationary Night Blindness), 603576 (TRPM1), 613216 (Congenital Stationary Night Blindness Type 1C), 601617 (RDH5), 603576 (SAG), 136880- Fundus Albipunctatus, 180380 (RHO), 610445 Autosomal Dominant Congenital Stationary Night Blindness 1 (CSNBAD1)

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:
NYX: X-linked recessive
TRPM1, RDH5, SAG: Autosomal recessive
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: NYX gene
DNA sequence is obtained and analyzed for the coding sequence and splice site junctions of the NYX gene (exons 1-2). 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 this gene.

Autosomal recessive CSNB: TRPM1, SAG and RDH5 genes
DNA sequence is obtained and analyzed for the coding sequence and splice site junctions of the 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 this gene.

**Autosomal dominant CSNB: RHO gene**
DNA sequence is obtained and analyzed for the coding sequence and splice site junctions of the RHO gene (exons 1-5).

**Test sensitivity:**

**NYX gene:** nystalopin
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.

**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).

**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 congenital stationary night blindness (CSNB) (Dryja et al., 1993; al-Jandal et al., 1999).

**Mutation spectrum:**

**NYX gene**
Missense, nonsense, frameshifts, and gross deletions have been reported.

**TRPM1 gene**
Missense, nonsense, frameshifts, splice site, and gross deletions have been reported.

**SAG gene**
Frameshift and nonsense mutations are the only types of mutation 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.

**RDH5 gene**
The vast majority of mutations observed in the RDH5 gene are missense mutations; however, frameshift mutations have also been observed.

**RHO gene**
The vast majority of mutations are missense changes that usually have a gain-of-function effect.

**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:** 20 mL amniotic fluid, 10 mg CVS, or 2 T25 flasks. Ship overnight at ambient temperature, using a cool pack in hot weather. Call to discuss requirements for parental blood. Keep backup cultures.

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

**Prices and Turn-Around Time - Fees are subject to change without notice:**
Test #431: NYX Mutation detection in a new male patient = $890; Approximately 7-8 weeks
Test #906: NYX deletion/duplication testing for females ONLY= $500; Approximately 3-4 weeks
Test #489: TRPM1 Mutation detection in a new patient = $3900; Approximately 8-9 weeks
Test #516: SAG Tier 1 c.926delA mutation ONLY = $350; Approximately 4 weeks
Test #517: SAG Tier 2: SAG: Sequencing remaining coding exons (2-10; 12-16) = $; Approximately 6 weeks
Test#427: RDH5 Mutation detection in a new patient = $770; Approximately 6-7 weeks
Test#298: RHO Mutation detection in a new patient = $770; Approximately 6-7 weeks
Test #901: Testing of a relative for a specific known mutation = $350; Approximately 2-4 weeks
Test #902: Prenatal diagnosis for a specific known mutation = $2000; Approximately 2 weeks

**CPT codes for mutation detection in a new patient - All codes and units apply:**

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**Possible ICD9 Codes:**
368.61 Congenital night blindness
368.63 Abnormal dark adaptation curve

**References Cited:**