Clinical Characterization and Linkage Analysis of a Family With Congenital X-Linked Nystagmus and Deuteranomaly

Mei L. Mellott, MD; Jeremiah Brown, Jr, MD; John H. Fingert; Christine M. Taylor; Ronald V. Keech, MD; Val C. Sheffield, MD, PhD; Edwin M. Stone, MD, PhD

Objectives: To identify a congenital nystagmus locus on the X chromosome and to characterize the phenotype of a 4-generation family affected with congenital nystagmus and color deficiency.

Methods: Sixty-five patients underwent an eye examination, including evaluation for the presence of nystagmus and color vision abnormalities. Affected patients and obligate carriers of the congenital nystagmus mutation were genotyped with short tandem repeat polymorphisms located on the X chromosome, and these data were subjected to linkage analysis.

Results: Fourteen patients were affected with a horizontal, conjugate, congenital nystagmus. All examined patients had a visual acuity of 20/60 or better. There were no associated ocular or systemic findings except that 18 of the family members had deficient red-green color vision, which was classified as deuteranomaly (the most common form of anomalous trichromacy). Five patients exhibited nystagmus and deuteranomaly. Significant linkage was demonstrated between the nystagmus phenotype and 11 markers from Xq. The maximum lod score was 4.84 ($\theta = 0$) and was obtained with marker DXS8041. Analysis of recombinants defined the disease interval to lie between markers ATAS9C05 and DXS1192 (a 5.4-centimorgan region). The proximity of this locus to the red-green opsin gene cluster (11 centimorgans more telomeric) explains the frequent coexistence of nystagmus and color vision deficiency in this family.

Conclusions: We have identified the genetic locus of the X-linked congenital nystagmus gene in this family. The critical interval in this report is less than half the size of the previously described nystagmus locus. These findings will aid in identifying the gene responsible for this condition.


Congenital nystagmus is a condition characterized by rhythmic eye oscillations that are present at birth or that develop in early infancy. It is an idiopathic condition that is presumed to be secondary to a defect in motor control of fixation. Congenital nystagmus is not uncommon, with an estimated frequency of 1 in 1500. Typical features of the condition include bilateral, conjugate, uniplanar, and usually horizontal eye movements, a null position that may be associated with a head turn, increased amplitude of the oscillations with fixation, and decreased amplitude with convergence. Visual acuity can be diminished by the decreased foveation time but is usually well preserved.

Congenital nystagmus can occur as an autosomal dominant, autosomal recessive, or X-linked trait. X-linked recessive inheritance has been suggested as the most frequent mode of inheritance. Two studies in the literature identified chromosomal loci associated with autosomal dominant congenital nystagmus: a balanced 7;15 translocation, and a linkage study implicating a locus on chromosome 6p12. Recently, linkage has been reported at 2 distinct loci in families with X-linked congenital nystagmus.

In this study, we describe a large, 4-generation pedigree with X-linked congenital nystagmus. The pedigree is unusual in that there is a frequent coexistence of deuteranomaly and nystagmus. Although 5% of human X chromosomes harbor recessive mutations that cause deuteranomalous color vision in men, the association of nystagmus and red-green color deficiency has been noted on only 1 previous occasion. In 1948, Rucker described a family with X-linked nystagmus in which a man with nystagmus and red-green color blindness had 2 affected daughters and an affected grandson.

In the present pedigree, we describe the clinical manifestations of congenital motor nystagmus and identify an interval containing the congenital nystagmus gene. We also
PATIENTS, MATERIALS, AND METHODS

Informed consent was obtained from all patients in the study. The presence of nystagmus was confirmed by slitlamp examination. Criteria for the diagnosis of congenital nystagmus included a history of nystagmus within the first 3 months of life and evidence of bilateral, conjugate, ocular oscillations by slitlamp examination. Sixty-five family members were examined by us (M.L.M., J.B., and R.V.K.). The medical records of 3 additional family members (2 of whom were deceased) were also examined. Screening examination included determination of visual acuity, slitlamp biomicroscopy, questioning about subjective photophobia or nyctalopia, and direct ophthalmoscopy. Color vision was evaluated using either Ishihara plates (Kanekura & Co Ltd, Tokyo, Japan) or standard pseudosochromatic plates (Ig-aku-Shoin, Tokyo). Selected patients also underwent Farnsworth-Munsell 100-hue testing, Nagel anomaloscope testing, or both to further characterize the color vision defect. To determine whether any retinal disease was associated with the nystagmus, dark adaptometry and electroretinography were performed on selected patients. Dark adaptation was evaluated with a Goldmann-Weckers dark adaptometer. Patients underwent 30 minutes of dark adaptation before electroretinography under full-field Ganzfeld dome stimulation (LKC Technology, Gaithersburg, Md) according to the International Society for Clinical Electrophysiology of Vision protocol.

Blood samples were obtained from affected family members and their parents, siblings, and spouses. Blood, 7 to 10 mL, was obtained from each patient in EDTA-containing glass tubes. DNA was prepared from the blood using a nonorganic method. Oligonucleotide primers flanking short tandem repeat polymorphisms located on the X chromosome were obtained from Research Genetics, Huntsville, Ala. Patients were then screened for variations in these X chromosome polymorphisms as previously described. Clinically normal women who were obligate carriers of the nystagmus mutation based on the existence of affected children were considered affected. Clinically normal female children of affected men were considered to have an “unknown” phenotype for the linkage analysis, unless they were obligate carriers.

Pairwise linkage analysis was performed with the MLINK and LODSCORE programs as implemented in the FASTLINK (version 2.3) version of the LINKAGE program package (available via the Internet at http://linkage.cpmc.columbia.edu/software/linkage). Allele frequencies were assumed to be equal for each marker. The true population allele frequencies for each marker could not be reliably estimated from the small number of spouses in the families. To show that the assumption of the equal allele frequencies would not affect our linkage results, we recalculated the lod scores using allele frequencies for the “affected” allele of 2 of the most tightly linked markers (DXS1047 and DXS8041), ranging from 0.01 to 0.50. The maximum lod score remained greater than 4 for each of these markers for all allele frequencies in this range. The genetic maps used for analysis of recombinants were obtained from the Marshfield Center for Medical Genetics, Marshfield, Wis, via the Internet at http://www.marshmed.org/genetics.

Figure 1. Pedigree. The left half of each symbol represents the clinical presence or absence of nystagmus, while the right half represents the status of the individual’s color vision. Solid symbols indicate individuals found to be clinically affected; open symbols, unaffected individuals; shaded symbols, individuals whose status could not be ascertained; open symbols with a black circle in the center, obligate carriers who are clinically unaffected; and slashed symbols, deceased individuals. All patients marked with a backward slash were examined by 1 or more of us (M.L.M., J.B., and R.V.K.). All patients marked with a forward slash were considered affected. Clinically normal female children of affected men were considered to have an “unknown” phenotype for the linkage analysis, unless they were obligate carriers. The affection status of the deceased individuals was obtained historically.

explore the relationship of the congenital motor nystagmus gene locus and the red and green opsin genes on Xq28 as an explanation for the coexistence of the 2 phenotypes in some members of this family.

RESULTS

CLINICAL FINDINGS

The pedigree structure and clinical features of each family member are summarized in Figure 1. Thirteen patients were found to have conjugate horizontal nystagmus. The waveform was pendular, jerk, or a combination of both waveforms. Examination of the medical records of 3 additional patients (II-5, III-6, and IV-13) revealed that they also had horizontal nystagmus. The visual acuity ranged from 20/20 to 20/60, and the decrease in visual acuity was proportional to the amplitude of the nystagmus. In most patients, the nystagmus had a null position in which the amplitude of the nystagmus was dampened. One family member (V-23) had undergone a Kestenbaum procedure at age 7 years for an abnormal head position associated with...
The nystagmus. No other neurologic disorders were present in any of the affected patients. No patients complained of photophobia. Direct ophthalmoscopy in all patients, and indirect ophthalmoscopy in selected patients, detected only 1 isolated fundus abnormality in the entire family, a choroidal hemangioma in patient V-8.

There were no subjective complaints of nystalgia. Dark adaptometry and electroretinography were performed on 8 patients to evaluate their retinal function. In particular, we attempted to rule out conditions such as cone dystrophy or congenital stationary night blindness, which could be associated with the type of nystagmus seen in this family. In 4 patients with nystagmus (V-1, V-3, III-3, and V-32) and 2 patients who were obligate carriers of the nystagmus gene (IV-10 and IV-12), the results of dark adaptation testing were normal, and the patients reached threshold after 15 minutes. Electroretinographic results were normal in these patients as well.

Of the 54 patients screened with pseudoisochromatic plates, 18 had color vision defects by color plate screening. Eleven of these patients (III-3, III-8, IV-6, IV-7, IV-9, IV-10, IV-11, IV-12, V-17, V-32, and V-40) were further characterized with the Nagel anomaloscope. All 11 patients were found to be deuteranomalous trichromats, with an average anomalquotient of 0.54 (mean, 24.42; range, 0-35; normal, 45). The matching range was narrow and extended from 0 to 30 on the red-green mixture scale. To further characterize the color defect, 7 patients (III-3, IV-10, IV-12, IV-16, V-32, V-39, and V-40) underwent Farnsworth-Munsell 100-hue testing under standardized conditions. A bipolar axis was evident with the highest error scores centered on caps 58 and 15, which is also characteristic of a deutan defect.

LINKAGE ANALYSIS

Forty-five family members (11 clinically affected, 9 obligate carriers, 13 clinically unaffected men, 10 unaffected women, and 2 informative spouses) were genotyped using short tandem repeat polymorphisms on the X chromosome. Two-point linkage analysis revealed significant linkage (lod score > 3) to 11 markers known to lie at Xq24 (Figure 2). The analysis of recombination events in affected individuals is also shown in Figure 2. These recombination events suggest that the X-linked nystagmus gene is located between markers ATAS9C05 and DXS1192. This interval lies approximately 11 centimorgans centromeric to the red-green opsin gene cluster.

Several recombination events between the nystagmus-causing gene and the red-green opsin cluster resulted in interesting patterns of inheritance. One woman (II-3) who is a carrier for the color vision abnormality and nystagmus had 1 son affected with deuteranomaly alone and a second who inherited both conditions. Haplotype analysis revealed a recombination event that caused 1 brother to “lose” the abnormal nystagmus gene. Similarly, siblings V-1 and V-3 are affected with only nystagmus. Individual V-1 manifests only nystagmus because she has 1 normal copy of the red-green opsin cluster that she inherited from her father. In contrast, her brother (V-3) manifests only nystagmus for a different reason. In this individual, a recombination event occurred between the nystagmus locus and the red-green opsin cluster, causing him to inherit only the nystagmus gene.

The inheritance pattern of the congenital nystagmus in this family is consistent with an X-linked gene that is completely penetrant in the hemizygous state and occasionally penetrant in the heterozygous state. X-linked recessive congenital nystagmus has been reported previously.16 The presence of affected women has been previously observed, and this phenomenon could in principle be ex-
plained by skewed lyonization. Patients V-1 and V-22 are interesting in this regard. Both of these women harbor an X chromosome with a nystagmus-causing mutation in coupling with a deuteranomaly-causing mutation. If skewed X inactivation were the explanation for the expression of this nystagmus, one might expect that they would exhibit deuteranomaly by the same mechanism. The normal color vision in these women suggests that other mechanisms are responsible for the variable penetrance of the nystagmus-causing mutation in heterozygotes. The concurrence of congenital nystagmus and deuteranomalalous trichromacy in this pedigree is a result of a recombination event inherited through the proband (III-3). The 2 traits have remained linked in most affected family members because of the proximity of the associated genes on the X chromosome. Linkage analysis places the X-linked congenital nystagmus locus at Xq24-q26, which is only 11 centimorgans centromeric to the red-green opsin gene cluster.14 Two loci for X-linked congenital nystagmus have been recently reported (Xp11.4-p11.3 and Xq26-q27).11,12 None of the pedigrees in these families exhibited deuteranomaly. The nystagmus locus identified in this study is contained within the previously reported Xq26-q27 locus and is 9.8 centimorgans smaller. These data confirm the presence of a nystagmus gene at this location and narrow the critical region.

In color matching tests, deuteranomalalous trichromats require more than the usual amount of green light to match a given test color. This phenotype is caused by mutations in a green-sensitive opsin gene on the X chromosome. The prevalence of deuteranomalalous trichromacy in women is 0.35%. This pedigree is interesting in that 5 of 7 of the proband’s daughters manifest deuteranomalalous color deficiency. This unusual occurrence can be explained by the presence of defective green opsin genes on each of their X chromosomes. Each daughter inherited the X chromosome that harbors a nystagmus-causing mutation and a defective green opsin gene from their father. Haplotypic analysis of the green opsin locus in this family revealed that the proband’s wife is also a carrier of a deuteranomaly-causing mutation and, furthermore, that each of the proband’s deuteranomaly-darling children inherited this paternal deuteranomaly allele. The high prevalence of deuteranomaly in the general population resulted in another initially confusing clinical observation, which was the presence of deuteranomaly in patient V-5. Haplotypic analysis of this patient revealed yet a third deuteranomaly allele in this family (inherited from his carrier mother).

The isolation of a locus for X-linked congenital nystagmus has clinical implications. In the evaluation of nystagmus in infants and children, the diagnoses of albinism, cone dystrophy, optic atrophy, and congenital stationary night blindness must be considered. In fact, several members of this family had been fully examined to rule out retinal disease. This study brings us closer to the identification of a gene responsible for X-linked congenital nystagmus. Identification of this gene will enable clinicians to accurately diagnose this form of congenital nystagmus with a simple genetic test. This will also enable the ophthalmologist to give accurate genetic counseling and to provide reassurance that affected individuals will not have notable visual impairment.

In summary, we describe an X-linked pedigree of congenital nystagmus that is linked to a 5.4-centimorgan interval on Xq24-q28. The location of the red-green opsin gene cluster at Xq28 explains the frequent coexistence of congenital nystagmus and deuteranomaly in this family.

Accepted for publication July 17, 1999.

This study was supported in part by the Carver Charitable Trust, Muscatine, Iowa; the Grousbeck Family Foundation, Boston, Mass; the Foundation Fighting Blindness, Baltimore, Md; grant EY10539 from the National Institutes of Health, Bethesda, Md; and an unrestricted grant from Research to Prevent Blindness Inc, New York, NY.

We thank all of the family members for participating in this study and Louisa Affatigato and Jean Andorf for their excellent technical assistance.

Reprints: Edwin M. Stone, MD, Department of Ophthalmology, The University of Iowa College of Medicine, Iowa City, IA 52242 (e-mail: edwin-stone@uiowa.edu).

REFERENCES