Nonprogressive congenital ataxia (NPCA) is a rare neurologic syndrome with both genetic and acquired causes. Clinically, patients present with developmental delay and truncal ataxia usually noticeable in the first year of life. About half of cases show cerebellar hypoplasia (particularly of the vermis) on MRI. Autosomal dominant, autosomal recessive, and X-linked inheritance have all been proposed, but no gene mutations have been identified. Recently, a large family with dominantly inherited NPCA and cognitive impairment was linked to an 8-cM region on chromosome 3p2 overlapping the spinocerebellar ataxia type 15 (SCA15) locus. Despite phenotypic heterogeneity, it is possible that SCA15 and autosomal dominant NPCA are allelic conditions.

Methods. We have followed a family with dominantly inherited NPCA originally reported in 1985. New clinical features have emerged, and two additional affected children have been born. The proband, now age 55, presented at age 24 complaining of dizziness and imbalance (II-1; table; figure 1). Although clumsy since childhood, she had normal developmental milestones and was an average student throughout high school. She initially exhibited a primary position upbeat nystagmus along with gaze-evoked nystagmus. There was mild truncal and limb ataxia without other neurologic findings. The primary position upbeat nystagmus disappeared in her early 30s, but she continues to have gaze-evoked nystagmus in all directions ( upbeat on up-gaze and downbeat on down-gaze). Also in her early 30s, the proband began experiencing episodes of ataxia typically triggered by exertion or stress. During these episodes that last from 15 minutes to 2 hours, she experiences vertical oscillopsia (like the vertical hold on a television is impaired, prompting her to replace her television set). The only findings on her most recent neurologic examination are stable mild truncal and extremity ataxia with mild dysarthria. A follow-up MRI scan of the brain showed mild vermian hypoplasia, unchanged from the MRI shown in the original report.

Follow-up neurologic examinations in the two affected daugh-

ters have shown a static ataxia syndrome, with spontaneous resolution of upbeat nystagmus in the primary position but persistent gaze-evoked nystagmus. Also, both daughters have developed episodes of ataxia with vertical oscillopsia, similar to the spells reported by their mother.

Both affected daughters have had an affected child since the original report. The 12-year-old son of III-3 (IV-3) was noted to have mild ataxia and incoordination during infancy, but had normal developmental milestones and has performed at an average level in regular school classes. The 4-year-old daughter of III-2 (IV-1) has had clear developmental delay and is showing early learning problems. When evaluated at age 26 months, a Griffith developmental assessment placed her at a 15-month level with a general development quotient of 57 (mildly retarded range). On examination, both IV-3 and IV-1 exhibit a primary position upbeat nystagmus, horizontal gaze-evoked nystagmus, and predominantly truncal ataxia with some mild extremity ataxia. An MRI scan of the brain in IV-3 showed mild vermian hypoplasia similar to that of other family members. The proband’s son (III-5) and the 5-year-old daughter of III-2 (IV-2) are asymptomatic with no ataxia.

Genomic DNA from each consenting individual was extracted from peripheral blood from consenting individuals, and the 10K mapping assay was performed and analyzed as previously described. This study was approved by the Institutional Review Board at UCLA.

Results. The panel of over 10,000 single-nucleotide polymorphisms (SNPs) was typed on all individuals in the family using the 10K SNP mapping assay. The data from this microarray-based approach were outstanding and resulted in high information content throughout the genome. The mean call rate was 97.27%, all DNA samples having over a 95% call rate (96.04 to 98.15%). Distribution of genotype calls was consistent over AA, AB, and BB calls showing slightly higher AB calls. Genotypes for SNPs with at least one Mendelian error were changed to “no call” across all the family members before starting the analysis. Total 79 such SNPs were zeroed out (0.09%). The genotype scan was run with Genehunter and Genechunter-Plus, a modified version of Genehunter 1.3 using a 40-marker window for parametric multipoint analysis. There were four regions with lod scores near 1.8 (penetrance 99%, gene frequency 0.001%) on chromosomes 1, 5, 7, and 9 (figure 2). These were the only regions that were near the maximum expected lod score for this family size and marker density. Haplotypes were constructed for all four regions using Merlin, and the recombination points were determined (Chr 1q44, bases 242, 106, 291-p ter; Chr 5q35.1-35.3, bases 171, 963, 046-p ter; Chr 7q36.2-36.3, bases 153, 486, 520-p ter; Chr 9q31.2-32, bases 105, 931, 673-111, 824, 195 by UCSC May 2004 assembly).
Discussion. In this follow-up study of a family with dominantly inherited NPCA originally reported in 1985, we have documented that the predominantly truncal ataxia is nonprogressive and that there is no change in midline cerebellar atrophy on follow-up MRI. Interestingly, family members that initially presented with primary position upbeat nystagmus now show only gaze-evoked nystagmus in all directions of gaze without primary position nystagmus. Also, these older family members have developed episodes of vertigo and ataxia with vertical oscillopsia, suggesting that they probably have transient episodes of the primary position vertical nystagmus along with baseline ataxia. Similar to other episodic ataxia syndromes, their episodes are triggered by exertion and stress.

This family with NPCA seems to be different from any previously reported family. The NPCA family linked to chromosome 3p had prominent learning problems in all affected family members and none had primary position nystagmus (only 1/20 had gaze-evoked nystagmus). Cognitive impairment is a prominent feature of most families reported with NPCA. There are no prior reports of NPCA with primary position upbeat nystagmus.

Although this study was based on a single small pedigree, the 10K SNP mapping assay proved to be very efficient, accurate, and rapid. This allowed us to make optimal use of linkage within this family and determine regions of the genome close to the maximum expected lod score. We ruled out linkage to the previously reported chromosome 3p locus for dominantly inherited NPCA and also ruled out linkage to loci reported with other dominantly inherited SCA syndromes. Interestingly, families with an autosomal recessive NPCA and a family with Joubert syndrome were previously linked to chromosome 9q, but the linked regions in these two families did not overlap the region on 9q found in our family.

We sequenced the EN2 gene because it is important for cerebellar development and resides in the critical region on chromosome 7q, but we found no mutations. With episodic features developing in the older affected family members, we considered genes encoding membrane proteins that regulate neuronal excitability as ideal candidates, as other episodic ataxia syndromes are channelopathies. However, in the candidate regions, there are no obvious ion channel genes expressed in the brain.

There are no additional relatives to expand the pedigree. As we systematically identify and sequence candidate genes in these regions, we hope that this report will stimulate the identification of other families with this distinctive phenotype to help narrow the candidate region.
References


