A New Dominant Spinocerebellar Ataxia Linked to Chromosome 19q13.4-qter

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Background: The autosomal dominant spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative disorders. Although molecular genetic studies have so far implicated 16 loci in the etiology of these diseases, approximately 30% of families with SCAs remain unlinked.

Objectives: To report the location of a gene causing a "pure" autosomal dominant cerebellar ataxia in one family and to describe the clinical phenotype.

Patients: We have identified a 4-generation American family of English and Dutch ethnicity with a pure cerebellar ataxia displaying an autosomal dominant pattern of inheritance. The disease typically has its onset in the third and fourth decades of life, shows no evidence of anticipation, progresses slowly, and does not appear to decrease life expectancy. Clinical DNA testing excluded SCA1, 2, 3, 6, 7, and 8.

Methods: A genome-wide linkage analysis at a 10 centimorgan (cM) level was performed with samples from 26 family members (11 affected, 10 clinically unaffected at risk, and 5 spouses).

Results: Assuming 90% penetrance, we found suggestive evidence of linkage to chromosome 19, with a lod score of 2.49 for D19S571. More detailed mapping in this region provided a maximum 2-point lod score of 2.57 at \( \theta = 0 \) for D19S254 and a maximum multipoint lod score of 4.72 at D19S926. By haplotype construction a 22-cM critical region from D19S601 to the q telomere was defined.

Conclusions: We have mapped a gene for an autosomal dominant SCA to chromosome 19q13.4-qter in one family. The critical region overlaps with the locus for SCA14, a disease described in a single Japanese family and characterized by axial myoclonus. Myoclonus was not seen in the family we studied, but it remains possible that the 2 disorders are allelic variants.

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The hereditary ataxias are a heterogeneous group of disorders characterized by slowly progressive incoordination of gait and poor coordination of hand and eye movements, associated with degeneration of the cerebellar cortex and spinal pathways. The hereditary ataxias can be subdivided by inheritance pattern, clinical differences, and pathologic findings. With increasing gene discovery, a molecular classification system has replaced the clinical one. The descriptive term spinocerebellar ataxia (SCA) is used to denote the progressive autosomal dominant entities, previously abbreviated ADCA. Molecular genetic studies have so far identified the loci responsible for SCA1 to 8 and SCA10 to 17. The most common genetic mechanism implicated in the etiology of SCAs is expansion of trinucleotide repeat sequences that leads to elongated polyglutamine tracts in the respective proteins. The SCAs are distinguished from the dominantly inherited episodic ataxias EA1 and EA2, which result from point mutations in ion channels, and dentatorubral-pallidoluysian atrophy, a disorder with a more complex phenotype. Two additional autosomal dominant complex disorders involving cerebellar ataxia have been identified. One of these disorders, sensory and motor neuropathy with ataxia, is characterized primarily by sensory ataxia, but affected individuals also have evidence of a motor neuropathy. Sensory and motor neuropathy with ataxia maps to chromosome 7q22.32. The other disorder, ataxia/pancytopenia, has prominent hematologic manifestations; this gene has not yet been localized.

In North American populations the known ataxia loci are not responsible for...
SUBJECTS AND METHODS

PEDIGREE AND CLINICAL FINDINGS

This is a 4-generation family of English and Dutch ethnic background with 14 affected family members, including 10 women and 4 men (Figure 1). Under protocols approved by the institutional review board of the University of Washington, Seattle, subjects were examined and blood samples were obtained from 24 members in 2 generations of the family. Ten subjects were affected. The pedigree demonstrates an autosomal dominant pattern of inheritance with evidence of male-to-male transmission. The clinical characteristics of this family are summarized in Table 1. Precise age at onset is difficult to estimate because of the subtle and slowly progressive nature of the symptoms. However, affected family members recalled the earliest symptoms of gait instability from ages 10 to 50 years, with a mean of 31 years. All affected persons had gait ataxia of a mild to moderate degree. No one required a wheelchair, but several older persons experienced frequent falls and used canes. Mild to moderate dysarthria was common, as was hand dysmetria with clumsiness of fine motor movements. Six persons had either horizontal jerk nystagmus or saccadic interruptions during smooth pursuit. Several persons had hypertensive tendon reflexes with one instance of Babinski response, but others had normal or hypoactive reflexes. No person had sensory loss, mental retardation, cognitive decline, or axial myoclonus. Life span did not appear to be decreased.

A typical affected family member was individual III:16. This 71-year-old man recalled clumsiness while running and frequent falls at approximately age 13 years. This impairment did not prevent him from physical activity and he became a lifelong golfer. He was a highly educated professional with a graduate degree. In his 40s he fractured both wrists in a fall, and at age 50 years he fractured a vertebral body in a fall while climbing stairs. On neurologic examination at age 65 years, his mental status was entirely normal. His positive findings were moderate wide-based gait ataxia with inability to tandem walk, moderate dysarthria, full eye movements with mild horizontal jerk nystagmus, dysmetria on finger-to-nose testing, hyperactive ankle reflexes, and a right Babinski reflex. Results of sensory testing were unremarkable, and he had no parkinsonian features. A magnetic resonance image at age 66 years showed midline cerebellar atrophy (Figure 2). In the past 5 years his gait had deteriorated and he often used a cane.

Family member II:7 (mother of III:16) died suddenly at age 66 years of a ruptured left middle cerebral artery aneurysm. Microscopic slides from her autopsy were available for review. The cerebellar cortex showed patchy Purkinje cell loss with empty baskets but no proliferation of Bergmann astrocytes (Figure 3). The granule cell layer was unremarkable. The medulla showed mild gliosis in the inferior olives without appreciable neuronal loss. The basis pontis, basal ganglia, and cerebral cortex were unremarkable, other than the acute hemorrhage.

No asymptomatic obligate carriers were observed, nor was there evidence of genetic anticipation. Clinical DNA testing in one affected family member did not identify a trinucleotide expansion in the genes for SCA1, 2, 3, 6, 7, or 8.

DNA ANALYSIS

DNA was extracted from leukocytes or Epstein-Barr virus-transformed B-lymphoblastoid cell lines as previously described. To identify the locus responsible for the phenotype in our family, we performed a whole genome linkage analysis at the 10 centimorgan (cM) level, using the same methodology as recently described. For the region of interest, additional polymorphic markers were identified from the Marshfield genetic map and obtained from Research Genetics (Huntsville, Ala). One primer of each pair was end-labeled with [γ-32P]phosphorus by a T4 kinase reaction. DNA amplification and product scoring were performed as previously described.

LINKAGE ANALYSIS AND HAPLOTYPE CONSTRUCTION

Power analysis and 2-point linkage analyses were performed with the SLINK and the MLINK subprograms of the LINKAGE package version 5.1 as previously described. For regions with 2-point lod scores greater than 0.5, multipoint analyses and haplotype reconstruction were performed with GENEHUNTER (version 1.2). For the region of interest not excluded by these analyses, VITESSE was used to compute the maximum multipoint lod score. Haplotypes were also constructed manually. Sex-averaged map distances used were described by Broman et al and are available from the Marshfield Web site.

RESULTS

Assuming a disease frequency of 0.00001, 90% penetrance, and 4 alleles of equal frequency, a simulation study using SLINK and 200 iterations suggested that a maximum lod score of 5.06 at a recombination fraction, θ, of 0.00 could be obtained with the available samples. These conditions gave a 41.5% chance of obtaining a lod score greater than 3.0. Using the same penetrance estimate, a whole genome scan across all 22 autosomes with 355 microsatellite markers at a 10-cM level found suggestive evidence of linkage to chromosome 19, with a lod score of 2.49 for D19S571 at θ=0.00. In addition, there were 2 loci with lod score greater than 1.0 and less than 2.0 and 8 loci with lod score greater than 0.5 and less than 1.0. Multipoint and haplotype analyses indicated that these other signals were false positives. More detailed mapping in the chromosome 19 region provided a maximum 2-point lod score of 2.57 at θ=0.00 for D19S254 (Table 2). Multipoint analysis including all subjects and
10 markers yielded a maximum lod score of 4.72 at D19S926 (Figure 4), corresponding to 100.01 KcM (Kosambi centimorgans) on the Marshfield sex-averaged map. By haplotype construction, a 22-cM critical region from D19S601, in band 19q13.4, to the q telomere cosegregating with the disease was defined. All the affected individuals carried the disease-associated haplotype (Figure 1).

We have described a family with SCA mapping to a locus in the telomeric segment of the long arm of chromosome 19. Clinically the family displays a pure form of cerebellar ataxia without any additional distinguishing features, such as mental retardation, cognitive decline, visual loss, myoclonus, or peripheral neuropathy. Of note,

Table 1. Clinical Characteristics*

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*DTR indicates deep tendon reflexes; MR, mental retardation; N1, normal; plus sign, present; minus sign, absent; upward arrow, increased reflexes; and downward arrow, decreased reflexes.

COMMENT
gene-rich chromosome 19 has already been implicated in 3 SCAs and the dominantly inherited episodic ataxia EA2. Spinocerebellar ataxia type 6 and EA2 are allelic variants resulting from a triplet repeat expansion and point mutation of the α-1A voltage-dependent calcium channel (CACNA1A) gene, respectively.\textsuperscript{15,16} CACNA1A maps to the p arm of the chromosome. Spinocerebellar ataxia type 13 was described in a single large French family and is clinically distinguished by the presence of mental retardation, not seen in our family.\textsuperscript{17} The SCA13 gene has not yet been identified, but according to the consensus National Center for Biotechnology Information (NCBI) maps, its location is centromeric to that found in our family. Spinocerebellar ataxia type 14 was described in a single Japanese family.\textsuperscript{18} In addition to cerebellar ataxia, this family manifested the unusual presenting finding of axial myoclonus. No gene is currently identified for SCA14, but its chromosomal location overlaps that of our family. Although different SCAs may be indistinguishable on the basis of clinical features, axial myoclonus has not been described with any other SCA and has not been observed in our family. No neuropathologic findings have been reported in many of the rare SCAs, including SCA13 and SCA14. The fortuitous, but limited, pathologic specimens in this family suggest a primary Purkinje cell defect.

Not surprisingly, given the large size of the critical region, query of the NCBI database,\textsuperscript{19} based on sequence information available on June 3, 2002, dis-
closed more than 250 genes mapped to the relevant region on chromosome 19q. Additional families with ataxia linked to this region and further recombination events are needed to narrow the critical region to make positional cloning efforts more feasible. Identifying the gene will facilitate our understanding of the neurodegenerative process and may lead to further experimental, diagnostic, and therapeutic strategies in neurodegenerative diseases.

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Author contributions: Study concept and design (Drs Brkanac, Raskind, and Bird and Ms Bylenok); acquisition of data (Drs Brkanac, Fernandez, Nochlin, Raskind, and Bird; Ms Bylenok and Lipe; and Mr Wolff); analysis and interpretation of data (Drs Brkanac, Raskind, and Bird, Ms Bylenok, and Mr Matsushita); drafting of the manuscript (Drs Brkanac, Raskind, and Bird); critical revision of the manuscript for important intellectual content (Mss Bylenok and Lipe; Drs Fernandez, Nochlin, Raskind, and Bird; and Mr Matsushita); statistical expertise (Mr Matsushita and Dr Raskind); obtaining funding (Ms Bylenok and Dr Bird); administrative, technical, or material support (Ms Lipe, Mr Wolff, and Dr Bird); study supervision (Drs Brkanac, Raskind, and Bird); and clinical evaluations (Dr Fernandez).

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We thank the many members of the family who participated in this research. We appreciate the assistance of James Cook. We want to thank the University of Washington Center for Human Development and Disability Genetics Core for the use of facilities and Jeff Goldy for technical assistance.

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REFERENCES

and cannot be found in the index. This is surprising for an entity that can potentially cause confusion between nonconvulsive status and metabolic encephalopathy.

Given the scope and breadth of this volume, there are very few errors. A few, however, stand out. The frequency of valproic acid–associated pancreatitis is given as 1% to 5% (page 456). However, the article cited for this estimate does not support such a high frequency and the current Physician’s Desk Reference (2002) estimates a considerably lower frequency of 2 cases per 2416 patients (~0.1%). Phenobarbital is described as “highly protein bound” and is grouped with phenytoin and valproic acid (page 527). Most authors would consider it an only moderately protein bound antiepileptic drug, and its impact, when protein binding kinetics are disturbed, would be considerably less than with either phenytoin or valproic acid. Finally, Neisseria meningitidis is a gram-negative, not a gram-positive organism (page 88), and venlafaxine is not considered a selective serotonin reuptake inhibitor (page 357).

Overall, this is a very useful, comprehensive, and authoritative text concerning a poorly represented yet critically important aspect of neurology and epileptology. It would be a welcome addition to any neurologist’s collection.

Mark Agostini, MD
Dallas, Tex

Correction

Error in Table. In the Original Contribution by Brkanac et al titled “A New Dominant Spinocerebellar Ataxia Linked to Chromosome 19q13.4-qter,” published in the August 2002 issue of the ARCHIVES (2002;59:1291-1295), an error occurred in a table. In Table 1 on page 1293, the column headings under “Pedigree No.” should have appeared as follows: III:2, III:4, III:10, III:14, III:16, IV:9, IV:12, IV:13, IV:15, and IV:16.