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Autosomal Dominant Spinocerebellar Ataxia with Sensory Axonal Neuropathy (*SCA4*): Clinical Description and Genetic Localization to Chromosome 16q22.1

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Summary

The hereditary ataxias represent a clinically and genetically heterogeneous group of neurodegenerative disorders. Various classification schemes based on clinical criteria are being replaced as molecular characterization of the ataxias proceeds; so far, seven distinct autosomal dominant hereditary ataxias have been genetically mapped in the human genome. We report linkage to chromosome 16q22.1 for one of these genes (*SCA4*) in a five-generation family with an autosomal dominant, late-onset spinocerebellar ataxia; the gene is tightly linked to the microsatellite marker D16S397 (LOD score = 5.93 at $\theta = .00$). In addition, we present clinical and electrophysiological data regarding the distinct and previously unreported phenotype consisting of ataxia with the invariant presence of a prominent axonal sensory neuropathy.

Introduction

Since Marie's (1893) description of an autosomal dominant ataxia distinct from Friedreich autosomal recessive ataxia, many ataxic syndromes with distinctive clinical features have been described. Based on clinical and pathological criteria, several classification schemes for the ataxias have been proposed (Holmes 1907; Greenfield 1954; Konigsmark and Weiner 1970; Harding 1984); none of these has proved completely satisfactory, because of the degree of phenotypic overlap between syndromes and because of the degree of clinical heterogeneity, even within families. All dominantly inherited ataxias cause some degree of clinical cerebellar dysfunction, although isolated cerebellar dysfunction is rare; to a varying degree, other components of the nervous system may be affected. One widely accepted clinical classification of autosomal dominant cerebellar ataxia (ADCA) relies on the presence of neuropathy, pyramidal signs, extrapyramidal signs, or ophthalmoparesis (ADCA I); the presence of retinopathy (ADCA II); or the absence of associated signs (ADCA III) (Harding 1993).

These autosomal dominant cerebellar ataxias are proving to be genetically heterogeneous, allowing molecular classification (Rosenberg 1995). The gene for spinocerebellar ataxia (SCA) type 1 (SCA1) has been mapped to chromosome 6p22-p23 (Ranum et al. 1991; Zoghbi et al. 1991), where an expanded CAG repeat has been found, in affected patients, within a gene for a novel protein (ataxin-1) (Orr et al. 1993; Banfi et al. 1994); although the function of this protein remains unknown, its distribution has been characterized in affected and control brains (Servadio et al. 1995). A second locus (SCA2), on chromosome 12q23-24.1, was mapped in a large Cuban pedigree with ataxia, ophthalmoparesis, and peripheral neuropathy (Orozco Diaz et al. 1990; Gispert et al. 1993). Machado-Joseph disease (MJD) and SCA3 have been shown to be due to an expanded CAG repeat sequence in a gene on chromosome 14q32.1 (Kawaguchi et al. 1994; Matilla et al. 1995); the mechanisms responsible for the phenotypic variation are unclear (Junck and Fink 1996). Other genetically mapped dominant ataxias include SCA5 on chromosome 11 (Ranum et al. 1994) and SCA7 on chromosome 3 (Benomar et al. 1995; Gouw et al. 1995) as well as dentatorubral-pallidoluysian atrophy (DRPLA), which is due to an expanded CAG repeat in a gene on chromosome 12 (Koide et al. 1994; Nagafuchi et al. 1994).

The gene defects responsible for three autosomal recessive cerebellar ataxias have also recently been characterized. Friedreich ataxia, in which ataxia is invariably accompanied by neuropathy and is often accompanied by cardiomyopathy, has recently been associated with an unstable GAA trinucleotide expansion in an intronic segment in a gene on 9q13 (Campuzano et al. 1996).

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An adult-onset spinocerebellar ataxia associated with low serum vitamin E levels has been demonstrated to be due to mutations in the alpha-tocopherol-transfer protein (Gotoda et al. 1995; Ouahchi et al. 1995). Ataxia telangiectasia has been shown to be due to a mutated gene, on chromosome 11q22-23, encoding a putative protein with similarities to phosphatidylinositol-3′ kinases (Savitsky et al. 1995).

We report a five-generation pedigree with late-onset, autosomal dominant cerebellar ataxia having distinctive associated clinical features of prominent axonal sensory neuropathy, areflexia, essentially normal eye movements, and extensor plantar reflexes. We have demonstrated linkage in this kindred to a genetic marker (D16S422) on chromosome 16q. Since our preliminary report regarding 12 affected individuals (Gardner et al. 1994), 9 additional affected individuals have been ascertained and studied by linkage analysis; refined linkage mapping now demonstrates linkage to the marker D16S397, with obligate recombinants placing the gene within a 6-cM region.

Subjects and Methods

Kindred and Clinical Findings

Thirty-eight family members of a five-generation pedigree (of Scandinavian origin and residing in Utah and Wyoming) were examined by at least one of the authors (K.A., K.G., and/or K.F.), and 20 met the disease criteria, defined as the presence of ataxia or dysmetria (fig. 1). An additional patient (individual 18956) included as affected had blood sampled for DNA 1 mo before her death in a nursing home, where she resided because of marked truncal instability and dyscoordination. Of the other affected patients, three (individuals 13299, 13289, and 13284) were classified as unaffected on initial exam 5 years prior to this report (at ages 30, 42, and 44 years, respectively) and were analyzed as such in our preliminary studies (Gardner et al. 1994); however, on reexamination 5 years later, these three had developed ataxia and/or dysmetria as well as neuropathy and are classified as affected for the purposes of this report. At the time of examination, gait or truncal ataxia was present in all affected individuals, except one who had limb dysmetria alone. Individuals $\leq$40 years of age were classified as unknown if they showed no signs of the disease.

Disease onset is typically in the 4th or 5th decade, but age-at-onset range was 19–59 years, with a median age at onset of 39.3 years. The earliest symptom is usually a gait disturbance, followed by difficulty with fine motor tasks and often by dysarthria. Ataxia progresses over decades, often leading to wheelchair dependence. At presentation, most did not complain of symptoms of neuropathy, although evidence of a length-dependent neuropathy could invariably be demonstrated on examination: all had vibratory and joint-position sense loss, and 95% had at least a minimal pinprick-sensation loss. All patients had absent ankle-jerk reflexes; knee-jerk reflexes were absent in 85%; and complete areflexia was seen in 25%. Extensor plantar responses were seen in 20%. Distal limb weakness was noted in four patients; proximal as well as distal limb weakness was noted in two patients, both of whom had extensor plantar responses, suggesting a pyramidal pattern of weakness. Dysarthria was present in 50%. Two patients had slightly saccadic visual pursuit, and one had occasional spontaneous lateral movements with visual fixation; eye movements were normal in the remainder of the patients. Clinical findings are summarized in the appendix.

Sensory-nerve conduction studies were carried out in 13 clinically affected patients. Sural sensory responses were absent in 12, and radial sensory responses were absent in 3; the 1 affected patient with a preserved sural nerve response (amplitude 11.2 μV) had a radial sensory response of decreased amplitude (2.4 μV). Vitamin E levels measured in two affected people were normal.

One family member (individual 22884) complained of difficulty walking, which had begun at age 62 years. He had been struck by lightning at age 20 years, struck by a train at age 27 years, and suffered pelvic-crush injuries in an industrial accident at age 50 years. He had absent leg reflexes and absent sural potentials but no dysmetria or truncal ataxia when examined at age 65 years and therefore did not meet disease criteria. However, his brother (individual 19138), who is clearly affected, had onset of symptoms at age 59 years; for this reason, we present linkage data below, with patient 22884 analyzed both as unknown and as affected. Because of our concern that the unexplained neuropathy present in individual 22884 might represent an incomplete expression of the disease phenotype, we examined his six children, ages 28–40 years. None had signs of ataxia, dysmetria, or neuropathy, and all were classified as unknown for the purpose of linkage analysis.

Anticipation in This SCA4 Family

Anticipation in disease onset has been described in several neurodegenerative diseases, including other forms of dominantly inherited ataxias. Several members of the fifth generation of our pedigree denied neurological symptoms but had clear signs of neuropathy and ataxia or dysmetria on examination, whereas the age at onset of symptoms was self-reported in all members of the fourth generation; thus, intergenerational comparisons of reported age at onset are confounded. When individuals denying illness but determined by examination to be affected were included, reliable ages at onset could be ascertained for nine individuals in each of the fourth and fifth generations. With these limitations regarding the data set, median age at onset was 41.9 years

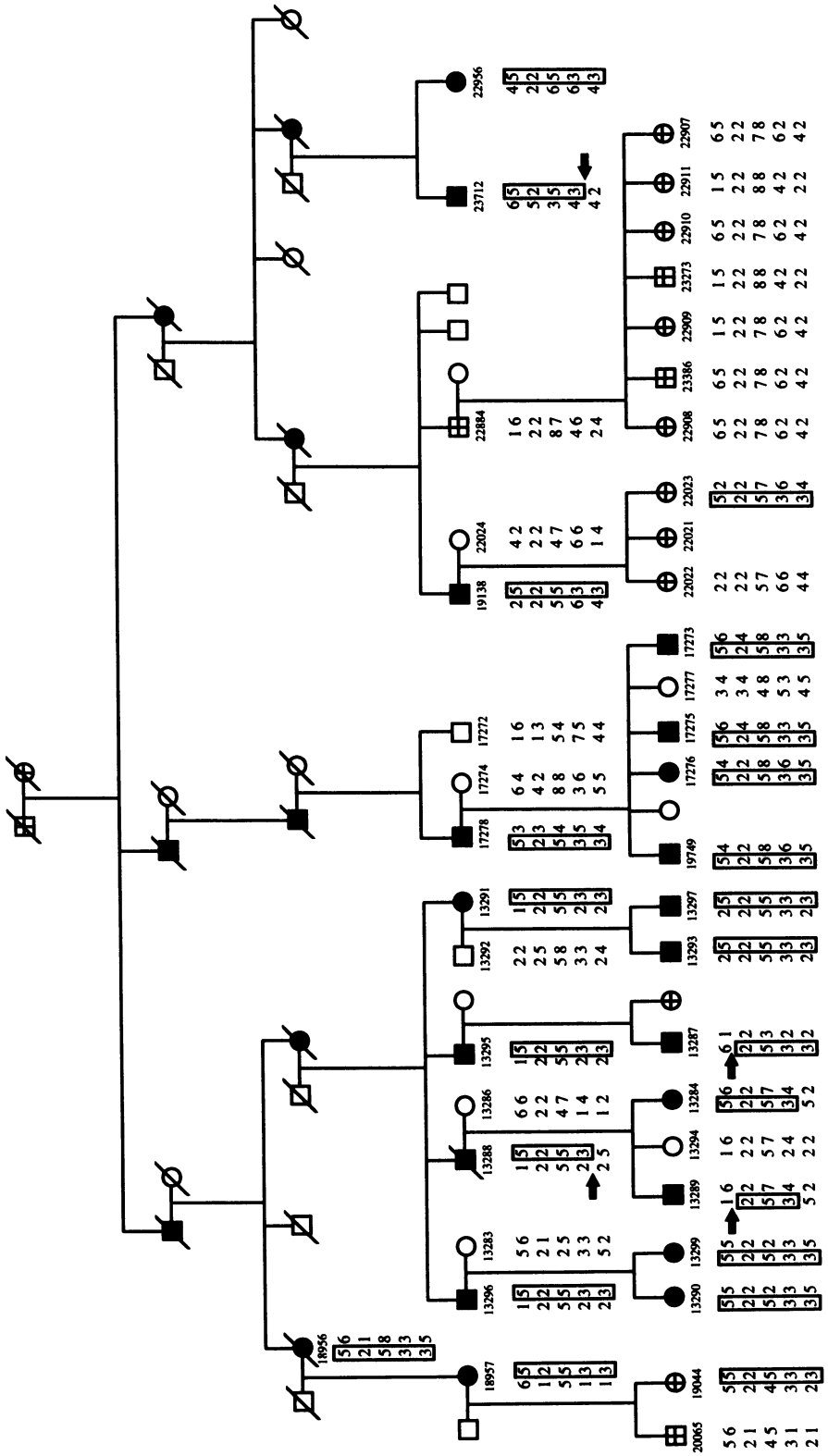

Figure 1 Kindred 1875 with genotypes for D16S514, D16S421, D16S398, D16S397, and D16S512 (top to bottom). Circles denote women, and squares denote men; blackened squares and circles denote affected individuals; and symbols containing crosses denote individuals classified as unknown (no clinical signs and age <40 years). A diagonal line through a symbol denotes that the individual is deceased. The genotypes are indicated under each individual. Arrows mark recombination events that define the disease gene–containing interval. One individual (individual 22023) analyzed as unknown carries the disease haplotype.

for the fourth generation and 36.7 years for the fifth generation.

Anticipation is suggested within some individual branches. Review of a neurologist's records showed that the deceased mother of patients 23712 and 22956 first noted gait difficulty at age 62 years, whereas her children noted gait difficulty at ages 25 years (individual 23712) and 45 years (individual 22956). Similarly, individual 17278 noted symptoms at age 45 years, whereas reported age at symptom onset in his children was 19–39 years. In contrast, individual 13288 reported symptoms at age 35 years, whereas his children denied symptoms but had demonstrable signs at ages 46 years (individual 13289) and 49 years (individual 13284).

Methods

DNA collection and isolation.—Anticoagulated venous-blood samples were obtained from 38 individuals. Patients or (in the case of minors) a responsible adult signed a "Consent for Participation" form approved by the Institutional Review Board for Human Research at the University of Utah School of Medicine. High-molecular-weight genomic DNA was isolated from whole-blood lysate with a phenol/chloroform extraction followed by isopropanol precipitation. Epstein-Barr–virus transformation of lymphoblastoid cell lines was accomplished as described elsewhere (Ptáček et al. 1991).

Microsatellite marker analysis.—Genetic evaluation of the kindred began with use of candidate markers linked to SCA1, SCA2, and the autosomal recessive Friedreich ataxia locus on chromosome 9q. After linkage was excluded for these loci by using markers D6S89, D12S79, D9S15, GS2, and GS4, a general linkage search was begun. DNA from an affected patient was also screened for the trinucleotide repeat expansions responsible for SCA1 and SCA3/MJD; these mutations were not found.

Highly informative polymorphic repeat CA markers spaced 30–50 cM apart were utilized in the general linkage search. Product size and annealing temperatures were considered when markers were multiplexed with PCR. End labeling of primers was performed as follows: 20 pmol of the forward primer, 50 mM Tris HCl, 10 mM MgCl2, 5 mM DTT, 16 units of polynucleotide kinase, and 7.0 μl of [γ^{32}P]ATP (5 mCi/ml) in a total volume of 10 μl. The mixture was incubated at 37°C for 30 min and then heated to 90°C for 2 min to inactivate the T_4 polynucleotide kinase.

Total genomic DNA was amplified with selected primers by using PCR. Each reaction included 50 ng of genomic DNA, 10 pmol of each primer (forward and reverse), 0.5 pmol of each end-labeled primer, 3 pmol of each deoxynucleoside triphosphate, 10 mM Tris HCl (pH 8.4), 40 mM KCl, 1.5 mM $MgC1_2$, and 0.5 units of *Taq* DNA polymerase in a total volume of 25 μl. PCR was performed under the following conditions: (1) 1 cycle at 94°C for 4 min; (2) 25 cycles, each at 94°C for 1 min, T_{anneal} for 1 min, 72°C for 1 min; (3) 72°C for 7 min; and (4) 4°C soak. After PCR, 10 μl of stop dye (98% formamide, 0.05% bromphenol blue, and 0.05% xylene cyanol with 20 mM EDTA) was added to each sample. Six to 12 microliters of each sample was loaded onto a 7% acrylamide gel containing 5.6 M urea, 32% formamide, 90 mM Tris borate (pH 7.5), and 2 mM EDTA. Gels were prerun at 80 W/gel for 1 h prior to loading and then electrophoresed at room temperature and constant power (80 W/gel) with 90 mM Tris borate (pH 7.5) and 2 mM EDTA running buffer. Gels were transferred to filter paper and were then exposed to X-ray film for 1–4 d at −80°C.

Linkage analysis.—Maximum-likelihood methods were used to perform pairwise two-point linkage analysis with MLINK of the LINKAGE program (Lathrop et al. 1985). Penetrance was set at .95, gene frequency at .001, for the disease allele.

Results

Linkage Analysis

We undertook a genomewide search for linkage, using regularly spaced, highly informative microsatellite markers. Autoradiograms were analyzed for genotypes of the 80 microsatellite markers. No incidence of misinheritance was noted with any of these 80 markers. With fewer (12) affected family members sampled, linkage to the marker D16S422 was established with a maximum LOD score of 4.08 at a recombination fraction (θ) of .00 (Gardner et al. 1994). As additional affected family members were added, the LOD score for D16S422 decreased to $-\infty$ at $\theta = .00$ and maximized at 0.99 ($\theta = .2$). Linkage mapping of nearby markers with the enlarged sample set (of all 21 affected patients) revealed the marker D16S397 to be linked to the disease allele, with a LOD score of 5.93 at $\theta = .00$. D16S397 is 26 cM from D16S422 (Gyapay et al. 1994). Table 1 shows pairwise linkage results between kindred 1875 and marker D16S397, over a range of θ's. Obligate recombinants are seen with flanking markers D16S514 and D16S512, defining a 6-cM interval within which the disease gene lies (figs. 1 and 2) (Gyapay et al. 1994). When individual 22884 is classified as affected, the maximum two-point LOD score is seen with marker D16S398 (LOD = 3.39 at $\theta = .05$).

Haplotype and Multipoint Analyses

Two other markers, D16S421 and D16S398, are inherited as a haplotype with D16S397 in affected individuals. The calculated recombination distance (from the Cooperative Human Linkage Center database [http://www.chlc.org]) between D16S397 and D16S421 is 0.00 with a LOD score of 31.61; between D16S397

Table 1

Pairwise Linkage Analysis of SCA4 Families, with Six Chromosome 16q Markers

	LOD Score at θ =						
Marker or Haplotype	.000	.01	.05	.1	.2	.3	.4
D16S514	−∞	2.66	3.56	3.53	2.79	1.72	.60
D16S421	2.57	2.52	2.33	2.06	1.51	.94	.41
D16S398	4.78	4.71	4.39	3.96	3.00	1.94	.83
D16S397	5.93	5.82	5.36	4.78	3.58	2.33	1.08
D16S512	−∞	3.06	3.97	3.94	3.21	2.14	.98
D16S422	−∞	−3.34	−.64	.40	.99	.88	.47
Haplotype D16S397/D16S398/D16S421	6.37	6.24	5.72	5.05	3.63	2.12	.67
	3.04	4.63	4.81	4.44	3.32	1.98	.65

Note.—Haplotype LOD scores underlined are calculated with individual 22884 classified as affected; all other scores are calculated with him classified as unknown (see the text).

and D16S398, the recombination distance is 0.00 with a LOD score of 43.05. With the three markers D16S397, D16S398, and D16S421 scored as a haplotype, two-point linkage analysis yields a LOD score of 6.37 at θ = .00; if individual 22884 is reclassified as affected rather than as unknown, the maximum LOD score remains highly significant (4.81 at θ = .05). These values did not change significantly when penetrance was decreased from .95 to .85.

Discussion

We have described a large family affected by cerebellar ataxia of variable age at onset (19–59 years), inherited as an autosomal dominant trait. The presence of associated neurological symptoms—in particular, neuropathy and extensor plantar responses—places this phenotype within the ADCA I category of Harding, along with the phenotypes associated with the *SCA1*, *SCA2*, and *SCA3/MJD* genes.

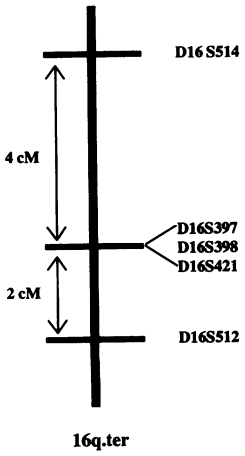

Figure 2 Map representing the interval containing the *SCA4* gene

The striking feature of the patients whom we describe is the invariant presence, in addition to ataxia, of a primarily sensory axonal neuropathy. Although the patients often denied symptoms of sensory loss, clinical signs were demonstrated in every patient, and electrophysiological corroboration could be obtained in every patient tested by nerve conduction studies. Notably, one 33-year-old individual carrying the disease haplotype but lacking clinical signs (individual 22023) has a decreased sural nerve sensory action potential amplitude (7 μV); her 36-year-old sister (individual 22021), from whom DNA was not obtained, also lacks clinical signs of neuropathy or ataxia and has no measurable sural response. Both are categorized as unknown for the purpose of linkage analysis, but the presence of these abnormalities suggests that subclinical neuropathy may be the earliest sign of the disease. Other signs—including areflexia, dysarthria, and extensor plantar responses—are more variable.

The universal presence of neuropathy and essentially normal eye movements helps to distinguish SCA4 from other forms of autosomal dominant cerebellar ataxia, in which neuropathy is seen as a less prominent feature. Prior to the availability of genetic classification, neuropathy was reported in association with spinocerebellar degenerations; electrophysiological evidence of neuropathy was demonstrated in some patients without clinical evidence of neuropathy (McLeod and Evans 1981). Reports since the availability of molecular classification have confirmed the association of neuropathy and spinocerebellar degeneration. In SCA1, vibration loss is seen in 51% of patients (Giunti et al. 1994), reflexes are increased (in 31%–67% of patients) more often than they are decreased (in 5%–15%) (Giunti et al. 1994; Dubourg et al. 1995), and ophthalmoplegia is promi-

nent (in 22%–63% of patients). In SCA2, vibratory loss is present in 10.6% of patients, and decreased reflexes are more common than increased reflexes (63.5% vs. 34.6%); ophthalmoparesis and slowed saccades are common (Orozco Diaz et al. 1990). Ankle hyporeflexia is reported as common in both the SCA3 and MJD phenotypes associated with the SCA3/MJD trinucleotide repeat expansion (Matilla et al. 1995); notably, our patients lacked the extrapyramidal features common in MJD. Another as-yet-unmapped ADCA, common in India, has a prominent neuropathy associated with hyporeflexia in 55% of patients and with vibratory loss in 27.5% (Wadia and Swami 1971; Wadia 1984). The distinguishing feature, however, is slowed saccadic eye movements, seen in 92.5% of patients; in contrast, some slowing of saccades was seen only in the late stages of illness in severely affected family members. Other minor abnormalities of eye movements included mildly saccadic pursuit (in two patients) and poor fixation (in one patient).

Phenotypically, the patients whom we report are most similar to a small French-German family (Biemond 1954) in which 6 of 17 members were affected in a late-onset, autosomal dominant pattern of ataxia and areflexia, as well as severe dorsal column sensory loss with corresponding pathological changes. Our patients' phenotype shares some similarities with Friedreich ataxia, in which neuropathy is always present; this similarity led to several of our patients being diagnosed with Friedreich ataxia at some point in their course of illness. Friedreich ataxia, however, is a recessive illness of generally early onset and is associated with cardiomyopathy.

Although anticipation in disease onset is not as clear in our family as in some other forms of SCA (Schut 1950; Coutinho and Andrade 1978; Zoghbi et al. 1988; Auburger et al. 1990; Ranum et al. 1994; Gouw et al. 1995), it is suggested in at least some branches of the family. We cannot confidently predict the presence of a dynamic mutation such as the trinucleotide repeat expansions demonstrated in other dominantly inherited ataxias (SCA1, SCA3/MJD, and DRPLA), but the possibility of such a mutation must be considered.

One candidate gene mapping in the 2-cM interval between D16S421 and D16S512 is a Na^+/H^+-exchanger isoform (NHE5), expressed in brain, spleen, testes, and skeletal muscle (Klanke et al. 1995). Na^+/H^+ exchangers are membrane proteins that mediate the exchange of extracellular Na^+ for intracellular H^+. Members of this protein family play a role in intracellular pH and cell-volume regulation, and a defect in function might conceivably lead to cell death. Experiments are underway in our laboratory to test this hypothesis.

The family that we report represents a distinct ataxic syndrome with universal, early, and prominent neuropathy in association with near-normal eye movements. Discovery of the gene defect will likely shed light on the pathophysiology of the cerebellum and of the dorsal root ganglia and may lead to further experimental, therapeutic, and diagnostic strategies in the study of this and other neurodegenerative diseases.

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Appendix

Summary of Clinical Findings in SCA4

Median age at onset	39.3 years
Fourth generation	41.9 years
Fifth generation	36.7 years
Gait ataxia	95%
Limb dysmetria	95%
Decreased sensation	100%
Vibration	100%
Pinprick	95%
Reflex abnormalities	100%
Absent ankle jerks	100%
Absent knee jerks	85%
Complete areflexia	25%
Dysarthria	50%
Distal weakness	20%
Babinski signs	20%
Oculomotor signs	15%
Nerve conduction studies (13 patients):	
Absent sural sensory-nerve action potentials	12/13

Percentages are of the 20 affected patients examined.

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