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Autosomal dominant cerebellar ataxia with retinal degeneration:
Clinical, neuropathologic, and genetic analysis of a large kindred

L.G. Gouw, BA; K.B. Digre, MD; C.P. Harris, MD; J.H. Haines, MD; and L.J. Ptacek, MD

Article abstract—The autosomal dominant cerebellar ataxias (ADCA) comprise a heterogeneous group of neurologic disorders characterized by degeneration of the cerebellum, spinal cord, and brainstem. Genetic analysis has revealed two loci, *SCA1* on chromosome 6p, and *SCA2* on chromosome 12q, responsible for some ADCA. We present a four-generation kindred of 42 individuals, 12 of whom were clinically affected with ADCA and an associated cone dystrophy. Early loss of color discrimination with retinal and macular signs is followed by gradual progression of cerebellar dysfunction and development of pyramidal signs. Pathology shows degeneration of cerebellum, basis pontis, inferior olive, and retinal ganglion cells. For genetic analysis, we used polymorphic markers D6S89 and D12S79; linkage analysis gave negative results, excluding linkage to both *SCA1* and *SCA2*. The data strongly support genetic heterogeneity consistent with the unique clinicopathologic features of the form of ADCA displayed in this large family.

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Autosomal dominant cerebellar ataxias (ADCA) include an array of clinical presentations: phenotypes include ataxia, dysarthria, dysmetria, dysdiadochokinesia, and intention tremor. There is progressive degeneration of the cerebellar cortex, and in certain subtypes, associated degeneration occurs in other structures including the cerebellar nuclei, basis pontis, inferior olivary nuclei, spinal cord, peripheral nerves, basal ganglia, optic nerve, and retina. The nosology is further complicated by variability in severity, age at onset, and progression, even within families. There are various schemes of clinical classification using a variety of criteria,[1-3] but none has been found wholly satisfactory, as all relate to phenotypes that are clinically heterogeneous. A more precise resolution of the underlying cause of the specific disorders requires characterization at the genetic and molecular level.[4] Recent linkage studies are beginning to unravel the tangled and often overlapping array of ADCA classification schemes; in a number of kindreds affected status can be associated with a specific genomic site. Currently, disease loci for ADCA designated "spinal cerebellar ataxia 1 and 2" (*SCA1* and *SCA2*) have been localized. *SCA1* lies on the short arm of chromosome 6 and is associated with a

number of families with ADCA.[5,6] A large Cuban kindred with features clinically indistinguishable from *SCA1* families exists[7]; the disease locus in this family, *SCA2*, lies on the long arm of chromosome 12.[8]

A form of ADCA exists that is clinically similar to *SCA1*- and *SCA2*-linked families but is distinguished by associated macular and retinal degeneration, manifested as early loss of color discrimination followed by progressive ataxia and loss of vision. Since its initial description as a distinct clinical entity,[9] a number of families showing concurrent spinocerebellar and retinal degeneration have been described.[10-16] We present a large family with this form of ADCA and describe clinical and pathologic findings, along with results of pairwise linkage analysis with genetic markers associated with *SCA1* and *SCA2*.

Methods. *Kindred.* Observations are based on kindred 1793, a family of four generations with 55 members. Forty-two of these family members were examined by one of the authors (K.D., J.H., or L.P.). Family members underwent a complete general neurologic examination, particularly of extraocular muscle and cerebellar function, with special attention to saccades, visual pursuit, appendicular coordination, rapid alternating movements, gait, and Romberg test-

ing. A complete eye examination was performed for all affected or at-risk individuals and included visual acuity measured with the Snellen eye chart and color vision assessment with the Farnsworth dichromatous (D15) standardized color-chip test and color plates. Retinal examination included both direct and indirect ophthalmoscopy, macular and retinal photographs, and whenever possible, electroretinography (ERG). The pedigree is shown in figure 1. A detailed family history was obtained through personal interviews with available family members. Twelve were clinically affected. Because of the variable onset of this disorder, at-risk family members were considered unaffected only if neurologic and ophthalmologic examinations were completely normal after age 50. Only one at-risk family member met these criteria (13218). Spouses marrying into the family were also considered unaffected. For the purpose of linkage analysis, the affection status of asymptomatic at-risk individuals under the age of 50 was considered unknown.

Anticoagulated venous blood samples obtained from the examined individuals were used for direct DNA preparations and to establish lymphoblastoid cell lines by Epstein-Barr virus transformation as previously described.[17] Subjects (or, in the case of minors, the responsible adult) signed a "Consent for Participation" form which was approved by the Institutional Review Board for Human Research at the University of Utah School of Medicine.

DNA isolation and marker analysis. High molecular-weight genomic DNA was isolated from whole blood lysate with a phenol/chloroform extraction followed by isopropanol precipitation.[18] Genetic evaluation was undertaken in the four-generation kindred using markers that are tightly linked to the *SCA1* and *SCA2* loci. End-labeled primers (D6S89a or D12S79a) were prepared as follows: 25 pmol primer, 50 mM TRIS HCl, 10 mM $MgCl_2$, 5.0 mM dithiothreitol, 8.4 U of T_4 polynucleotide kinase, and 6.0 µl [γ-^{32}P] ATP (5 mCi/ml), in a total volume of 10 µl. This mixture was incubated at 37 °C for 30 minutes and was then heated to 95 °C for 2 minutes to inactivate the T_4 polynucleotide kinase.

The polymerase chain reaction (PCR) was used to amplify total genomic DNA using primers flanking polymorphic regions known to be tightly linked to loci associated with ADCA. The reaction mixture contained 100 ng of genomic DNA, 10 pmol of each primer (D6S89a and D6S89b, or D12S79a and D12S79b), 1 pmol of the end-labeled primer (D6S89a or D12S79a), 2.5 nmol of each deoxynucleoside triphosphate, 10 mM TRIS HCl (pH 8.4), 40 mM NaCl, 1.5 mM $MgCl_2$, and 0.5 U *Taq* DNA polymerase in a volume of 25 µl. PCR was carried out under the following conditions: (1) one cycle at 94 °C for 4 minutes; (2) 30 cycles, each at 94 °C for 1 minute, T_{anneal} for 1 minute, and 72 °C for 1 minute; and (3) cooling to 4 °C. T_{anneal} was 54 °C for D6S89 and 58 °C for D12S79. After

Table 1. Clinical features of ADCA kindreds

Clinical features	Kindred 1793	SCA1 kindreds[5,6]	SCA2 kindred[7]
Age at onset (range)	(12-53)	(15-35)[6] (26-59)[5]	(2-65)
Average duration of disease	Highly variable Maximum observed, 35 years	13.1[6] 25.4[5]	Variable (7-20) Maximum observed, 47 years
Ataxia	+	+	+
Dysmetria	+	+	+
Dysathria/Dysphagia	+	+	+
Retinal/Macular degeneration	+	−	−
Eye movement abnormalities	Slow saccades, ophthalmoparesis	Ophthalmoparesis/nystagmus,[6] occasional nystagmus[5]	Slow saccades, ophthalmoparesis
Extrapyramidal signs	−	+[6] −[5]	−
Reflexes Hyper Hypo	Babinski present + +	Babinski present + +[6]/−[5]	+ +
Posterior column sensory deficit	−	+	+
Dull mentation	−	−[6] +[5]	−
Pathology	Atrophy of Purkinje cells, granule cells, dentate nuclei, inferior olive, basis pontis, retinal ganglion cells, lateral geniculate nuclei, spinocerebellar tracts, and middle cerebellar peduncle; mild loss of posterior funiculus and substantia nigra	Atrophy of Purkinje cells, cerebellum, inferior olive; variable pontine and spinal cord involvement; changes in spinocerebellar tracts, posterior funiculus, and CN IX, X, and XII nuclei[6] Atrophy of Purkinje cells, white matter of cerebellum, inferior olive, basis pontis, CN XII nuclei, dorsal columns, and spinocerebellar tracts[5]	Atrophy of Purkinje cells, esp. neo/paleocerebellar cortices; dentate nuclei intact; atrophy of inferior olive, pontine nuclei, substantia nigra; marked demyelination of posterior funiculus, moderate loss of spinocerebellar tract[27]

+ Present.
− Absent.

PCR, 5 µl of stop dye (98% formamide, 0.05% bromophenol blue, 0.05% xylene cyanol, and 20 mM EDTA) was added. Four µl of each sample were then loaded on a 7% acrylamide gel that contained 5.6 M urea, 32% formamide, 90 mM TRIS borate (pH 7.5), and 2 mM EDTA. Pre-electrophoresis of gels (1 hour prior to loading) and electrophoresis were performed at room temperature and at constant power (80 W/gel) with 90 mM TRIS borate (pH 7.5) and 2 mM EDTA running buffer. Gels were placed on filter paper and exposed to x-ray film overnight at −80 °C. Autoradiograms were analyzed for genotypes of the polymorphic alleles. With D6S89, nine alleles were observed between 199-225 bp. D12S79 showed seven alleles between 149-169 bp.

Statistical analysis. Using maximum-likelihood methods, we performed pairwise linkage analysis with the MLINK program of the LINKAGE system.[19] We calculated two-point analysis of the markers to the disease locus at a penetrance of 0.95. A gene frequency of 0.001 was assigned to the disease allele and 0.999 for the normal allele.

Results. *Clinical findings.* Clinical features are summarized in table 1. For comparison, clinical features are also shown for patients in ADCA kindreds known to be linked to *SCA1* and *SCA2*. Three patients with different stages of disease are described, illustrating the range and clinical variation in severity, age at onset, and progression.

Patient 13180. The proband first noted visual loss at age 13. By age 16, she began to have problems with stability and balance. This progressed to the point where a wheelchair was required at age 25. Physical examination at age 28 showed visual acuity without correction to be limited to only light perception; pupils were 8 mm in darkness bilaterally and 7 mm in light bilaterally, showing no relative afferent pupillary defect. She had 45 diopters of exotropia by the Krimsky rule. Extraocular motility was markedly diminished in all directions except downgaze, where moderate limitation was noted. A Bell's phenomenon was demonstrated, which showed better up-gaze
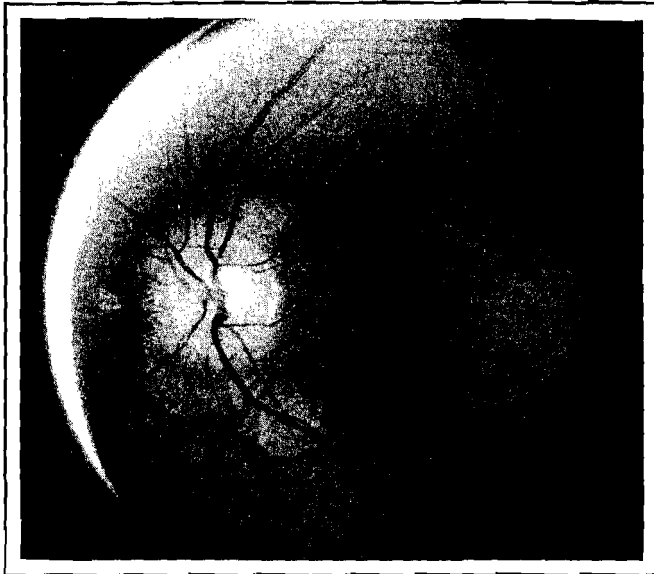
Figure 2. Funduscopic photo of the proband (13180) shows changes seen in the late stage of the disease. There is extreme macular degeneration with rare dot hemorrhages.

than voluntary gaze. ERG testing showed absent A and B waves. Slit-lamp examination disclosed a normal anterior segment. The fundus showed large atrophic areas in the macula and rare dot hemorrhages adjacent to the arcades surrounding the macula (figure 2). Saccades were markedly slow. Slight weakness in eye closure and hyperactive gag were noted. Muscle tone was markedly increased, with motor strength rated 5/5. Upper-extremity reflexes were +3 to +4 with bilateral ankle clonus and tonic bilateral Babinski signs. Finger-to-nose was slow and ataxic, heel-to-shin was completely dysmetric, and alternating rapid movements were slow and ataxic bilaterally. Speech was markedly dysarthric. Sensation was normal throughout. By age 29, there was minimal pupillary light reflex with virtual absence of extraocular movements. Disks showed pallor and large atrophic scars around the macula. Examination demonstrated bilateral facial weakness and truncal titubations. She died at the age of 31 of pneumonia and respiratory compromise secondary to progression of the disease.

Patient 13174. The father of the proband first noted an episode of double vision at age 30. Subsequent visual examination showed acuity of 20/25 bilaterally with correction; night vision was less impaired. Progressive photophobia was noted. At age 33 he noted ataxia, particularly when running, which progressed to frequent stumbling and awkward gait while walking. Around this time he also noticed speech difficulty, speaking in a hoarse whisper with progressive dysarthria. He denied hearing problems, dizziness, numbness, or paresthesia. Physical examination at age 58 showed visual acuity of 20/400, which could be corrected to 20/300 in both eyes. Color-plate testing revealed inability to see any color and on D15 testing, ability to see only a mixed shade of gray. Pupils were 6 mm and sluggishly reactive to light. Extraocular movements were impaired, especially up-gaze. Vestibular ocular reflex was intact. Pursuit was fair, but saccades were slowed. Visual fields were full to confrontation in the periphery, with central scotoma. Slit-lamp examination disclosed mild nuclear sclerosis. Corneal reflex was present but gag reflex was decreased bilaterally. Motor strength was normal

with increased tone; reflexes were hyperactive, and ankle clonus was present bilaterally. Babinski and Hoffman signs were present. Marked dysdiadochokinesis, impaired rapid alternating movements, and heel-to-shin ataxia were present. Funduscopic examination revealed disk pallor and granular changes in the macula. ERG showed absent photopic response and a present but reduced scotopic response.

Patient 13271. The sister of the proband noticed increasing vision problems primarily characterized as difficulty with driving and seeing signs at age 29. By age 30 she noticed problems with her gait, especially after prolonged inactivity. Physical examination at age 31 showed best corrected visual acuity to be 20/60-2 and 20/70-2. Color-plate acuity was significantly reduced bilaterally. D15 color testing showed a defect in the tritan axis. Fields were normal, extraocular movements were full, and fundus was normal. Saccades were slowed. Reflexes were brisk but no clonus was present. Plantar reflexes were equivocal. Motor strength was normal. Finger-to-nose and heel-to-shin were fair, and rapid alternating movements were good. A hint of dysarthria was noted in her speech. Tandem gait was normal, but she was somewhat clumsy in hopping on one foot. Visual field examination and ERG were entirely normal.

Autopsy findings. At autopsy of the proband, the most striking features were present upon neuropathologic examination. The cerebral hemispheres demonstrated no atrophy grossly. However, all of the posterior fossa structures were severely atrophic (figure 3), with the cerebellum, pons, and medulla being only about half of their normal expected size. Multiple coronal sections through the cerebral hemispheres were unremarkable, but axial sections through the cerebellum and brainstem revealed shrunken, discolored cerebellar folia, symmetric thinning of the middle cerebellar peduncles, and atrophic inferior olivary nuclei. The caliber of the spinal cord was also diminished.

Light microscopic examination with hematoxylin-eosin staining revealed normal cerebral cortices and basal ganglia. The lateral geniculate nuclei demonstrated severe neuronal loss and accompanying gliosis. Mild to moderate neuronal dropout was present in the substantia nigra with a reactive astrocytosis. Sections of the cerebellum confirmed near-total loss of the dentate nucleus neurons with an underlying gliosis. The cerebellar folia exhibited severe Purkinje cell loss with an accompanying Bergmann gliosis, granular cell dropout, and thinning of the white matter. The pontine tegmentum was normal, but the basis pontis was shrunken with diffuse loss of pontine neurons, and the white matter tracts were thinned. Near-complete loss of the neuronal population of the inferior olivary nuclei was seen with diffuse astrocytosis. Sections of the spinal cord demonstrated mild tract degeneration in the posterior columns and more significant loss of both dorsal and ventral spinal cerebellar tracts most prominent in the cervical region.

Sections of the eyes at autopsy showed a normal anterior chamber, iris, lens, and ciliary body. Poste-

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Figure 3. Gross section of the posterior fossa of the proband taken at autopsy shows striking atrophy. The patient's section at the top is contrasted with the age-matched control below, showing marked degeneration of the pons and anterior vermis. Shrunken, discolored cerebellar folia, atrophy of the inferior olivary nuclei, and diminished spinal cord caliber were also present grossly.

rior changes included numerous cobblestone-like, deep pigmented areas in a circumferential pattern at the level of the pars plana and ora serrata, some with a dark brown central pigment clump. No obvious retinal vasculature was apparent. The macula appeared to have a central cavity. The optic nerve head appeared very pale and atrophic.

Microscopic examination of the retina demonstrated diffuse, extensive degeneration of the photoreceptor cell layer, as well as absence of much of the outer nuclear layer throughout. Focal areas of abrupt discontinuity of the retinal pigment epithelium were noted. The choroid appeared to be uninvolved. The optic nerve showed early atrophic changes. Autopsy findings are summarized at the bottom of table 1 and contrasted with pathologic observations in kindreds linked to the SCA1 and SCA2 loci.

Genetic analysis. Linkage results between kindred 1793 and D6S89 (a chromosome 6p marker with 2% recombination with locus SCA1) and D12S79 (a chromosome 12q marker with 4% recombination with locus SCA2) are summarized in table 2. Pairwise log of the odds (lod) scores were calculated at a penetrance of 0.95. Lod scores are given for various recombination fractions for each marker under strict diagnostic criteria with 12 clinically affected, nine

Table 2. Log of the odds (lod) score table for pairwise linkage between kindred 1793 and markers known to be associated with autosomal dominant spinocerebellar ataxia loci SCA1 (D6S89) and SCA2 (D12S79)*

Marker	Lod score at recombination fraction						
	0%	1%	5%	10%	20%	30%	40%
D6S89	−1.34	−1.31	−0.81	−0.34	0.08	0.18	0.14
D12S79	−8.09	−5.00	−3.21	−2.03	−0.91	−0.41	−0.14
Simulation	3.37	3.31	3.06	2.75	2.06	1.33	0.60

* Results are based on a conservative estimate of disease frequency of 0.001. An assumed penetrance of 95% and sex-averaged recombination fraction were used. Family members' affection status is described in figure 1. Data assumes 12 affected, nine unaffected, and 21 unknown at-risk family members.

unaffected, and 21 individuals of unknown phenotype. Under these conditions, with 95% penetrance, lod scores for marker D12S79 are less than −2 from zero to 10% recombination, excluding the disease allele from a 20-cM region around the marker. Reducing the penetrance to 70% also gave consistently negative data (data not shown). In contrast, in a simulation run where the disease phenotype cosegregates with an optimal two-allele marker, a maximum potential lod score of 3.37 at zero recombination can be generated with kindred 1793. The disparity between the maximum potential lod scores and those generated by marker D12S79 indicates that linkage of the disease seen in kindred 1793 to SCA2 is highly unlikely. Although lod scores for marker D6S89 were greater than −2, all values remained negative from zero to 17% recombination. Furthermore, the existence of at least two obligate recombinants between the disease and a marker known to lie within 2 cM of SCA1 make linkage in kindred 1793 to this locus unlikely as well.

Discussion. Members of our four-generation family had ADCA and retinal degeneration. The disease was characterized by early visual deficits followed by deteriorating vision and progressive limb and gait ataxia. Investigation of the family outlined the spectrum of signs and symptoms from asymptomatic loss of color discrimination with macular signs to complete blindness and disabling ataxia. D15 color-chip testing demonstrated abnormalities in all affected individuals; the defects were all in the tritan color axis (yellow-blue), a very rare dichromatic deficiency. Other clinical manifestations included severe dysarthria, dysmetria, dysdiadochokinesia, ophthalmoplegia, and upper motor neuron signs. Severity and age of onset varied considerably. Anticipation may have been present, with earlier generations exhibiting milder signs and later onset and subsequent generations showing earlier onset with more dramatic changes.

Many of the posterior fossa findings were similar to those in other subgroups of multisystem atrophy. Pathology included neuronal loss in the inferior oli-

vary nuclei and basis pontis; cerebellar neuronal loss included Purkinje cells, granule cells, and neurons of the dentate nuclei. Corresponding tract atrophy included mild loss of the posterior funiculus of the spinal cord and more significant loss of the spino-cerebellar fibers and middle cerebellar peduncles. The distinctive feature of this ADCA subtype was the severe loss of the photoreceptor layer and ganglion cells in the retina along with atrophic changes of the optic nerve.

A number of families with ADCA are linked to HLA and genetic markers on the short arm of chromosome 6.[5,20-23] SCA1 is the designated disease locus for this form of spinocerebellar ataxia. SCA1 lies in region 6p23.05-p24.2,[24] within 2 cM of polymorphic marker D6S89,[25] a microsatellite GT-repeat useful for linkage due to its proximity, ease of PCR-based analysis, and high informativeness.[26] SCA1 is linked to families with ADCA without peripheral involvement as well as to families exhibiting a form of ADCA notable for associated cranial nerves IX, X, and XII palsies (olivopontocerebellar atrophy type IV, Schut-Haymaker type).[6] This implies two distinct disorders that are tightly linked and may be allelic. However, enough similarities exist between these families for variations in sampling between investigative groups to account for the described phenotypic differences.

Genetic analysis of other kindreds with members exhibiting a clinically indistinguishable form of ADCA[7,27,28] excluded linkage to SCA1,[28,29] providing evidence of genetic heterogeneity despite clinical homogeneity. Further studies with a large Cuban ADCA kindred[7,27] localized another disease locus, SCA2, to the chromosome 12q23-q24.1 region,[8] flanked by the phospholipase A2 gene and within 4 cM of another highly informative polymorphic marker, D12S79. A summary of clinical and pathologic features is outlined in table 1.

Two-point linkage analysis between the disease phenotype in kindred 1793 and the aforementioned markers, known to be associated with ADCA, gave negative lod scores for tight linkage to both D6S89 and D12S79. The data outlined in table 2 exclude the disease locus from both candidate regions on chromosomes 6p and 12q and provide evidence that the disease seen in kindred 1793 is a distinct entity both phenotypically and genetically, despite the many similarities in clinical presentation and pathology to SCA1- and SCA2-linked families. This is a necessary prelude for the eventual characterization of a third genomic locus associated with this unique clinico-pathologic presentation. Further genetic analysis should eventually yield a chromosomal region associated with the phenotype in kindred 1793. Numerous highly polymorphic PCR-based markers exist and new markers continue to become available, making a general linkage search of the entire human genome feasible with a well-defined kindred of this size.

The anticipation in this and other families with similar findings is interesting in light of discoveries that there is a genetic basis for this phenomenon in a number of inherited diseases, such as spinal bulbar muscular atrophy, fragile X syndrome, myotonic dystrophy, and Huntington's disease, in the form of generationally expanding hypervariable trinucleotide repeat regions.[30-35] Furthermore, the disease phenotype for SCA1-linked families is associated with an expanding trinucleotide repeat in the SCA1 region; the repeat is transcribed to a 10-kilobase mRNA product found in numerous tissues.[36] As in the other diseases associated with trinucleotide repeat expansions, the size of the expansion correlates with the severity of the disease. A similar region affecting cell-specific gene function or expression would explain the variable clinical presentation in this family and may aid in the isolation of the gene. Genetic characterization will not only allow for unambiguous classification of the disease entity and provide the basis for presymptomatic screening but should also provide valuable insight in the study of both spinocerebellar and retinal degeneration.

Acknowledgments

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