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Autosomal Dominant Cerebellar Ataxia Type III: Linkage in a Large British Family to a 7.6-cM Region on Chromosome 15q14-21.3

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Summary

Autosomal dominant cerebellar ataxia type III (ADCA III) is a relatively benign, late-onset, slowly progressive neurological disorder characterized by an uncomplicated cerebellar syndrome. Three loci have been identified: a moderately expanded CAG trinucleotide repeat in the SCA 6 gene, the SCA 5 locus on chromosome 11, and a third locus on chromosome 22 (SCA 10). We have identified two British families in which affected individuals do not have the SCA 6 expansion and in which the disease is not linked to SCA 5 or SCA 10. Both families exhibit the typical phenotype of ADCA III. Using a genomewide searching strategy in one of these families, we have linked the disease phenotype to marker D15S1039. Construction of haplotypes has defined a 7.6-cM interval between the flanking markers D15S146 and D15S1016, thereby assigning another ADCA III locus to the proximal long-arm of chromosome 15 (SCA 11). We excluded linkage of the disease phenotype to this region in the second family. These results indicate the presence of two additional ADCA III loci and more clearly define the genetic heterogeneity of ADCA III.

Introduction

Autosomal dominant cerebellar ataxias (ADCA) constitute a group of neurodegenerative disorders that can be classified clinically into three major categories (Harding 1993). ADCA type I (ADCA I) is characterized by ataxia variably associated with other neurological features, including involvement of the central and/or peripheral nervous system. Linkage studies identified four loci, on chromosome 6, 12, 14, and 16, and three genes, SCA 1 (MIM 164400), 2 (MIM 183090), and 3 (MIM 109150), have been cloned (Orr et al. 1993; Kawaguchi et al. 1994; Flanigan et al. 1996; Imbert et al. 1996; Pulst et al. 1996; Sanpei et al. 1996). ADCA type II (ADCA II; MIM 164500) is distinguished clinically by the presence of a pigmentary macular dystrophy (Harding 1982, 1993) and by the variability in the mode of presentation and striking anticipation. Affected individuals in most ADCA II families have a trinucleotide-repeat expansion in the SCA 7 gene (Giunti et al. 1999).

The focus of the present study is ADCA type III (ADCA III; MIM 117210), which is characterized by a relatively pure cerebellar syndrome and is genetically heterogeneous. To date, three loci have been identified. The SCA 6 (MIM 183086) CAG-repeat expansion (Zhuchenko et al. 1997) on chromosome 19 is responsible for ~50% of British ADCA III families (P. Giunti, P. F. Worth, M. G. Sweeney, and N. W. Wood, unpublished data). In addition, linkage of the disease phenotype in two families to loci on chromosome 11 (SCA 5; MIM 600224; Ranum et al. 1994) and chromosome 22q (SCA 10; MIM 603516; Zu et al. 1999) has been reported. The clinico-genetic classification of the ADCAs is summarized in table 1.

We have identified two British ADCA III families in which affected individuals do not have expansions in the SCA 1, 2, 3, 6, or 7 genes and in which the disease phenotype is not linked to SCA 4, SCA 5, or SCA 10. To identify the ADCA III loci in these families, we have used a genomewide linkage analysis. Here, we report evidence of linkage of the disease phenotype in one of these families to a novel locus on chromosome 15q and provide further evidence of genetic heterogeneity in this condition.

Families and Methods

This study was approved by the Ethics Committee of the Institute of Neurology. Informed consent was obtained from all individuals who participated.

Family 1

Figure 1 shows a simplified and abbreviated genealogical tree for family 1, with seven of the eight generations ascertained. Detailed clinical examination has

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Table 1

Clinico-Genetic Classification of ADCA

ADCA Type	Clinical Features	Genetic Loci and Chromosomal Location
I	Cerebellar syndrome plus pyramidal signs, supranuclear ophthalmoplegia, extrapyramidal signs, and dementia	SCA 1 6p22–23; SCA 2 12q23–24.1; SCA 3 14q32.1; SCA 4 16q24–ter
II	Cerebellar syndrome plus pigmentary maculopathy	SCA 7 3p12-21.1
III	"Pure" cerebellar syndrome; mild pyramidal signs	SCA 5 Cent 11; SCA 6 19p13; SCA 10 22q; SCA 11 15q14-21.3

NOTE.—SCA genes that have been cloned are underlined.

been done in 14 affected subjects. In each of the other three affected individuals, more than one family informant has confirmed affected status and has supplied age-at-onset data. DNA samples are available from 17 of 30 affected subjects, six at-risk subjects, and five unaffected spouses. There are no asymptomatic obligate carriers. Male-to-male transmission is observed in this family. Student's *t*-test was used for comparison of mean ages at onset.

Family 2

Family 2 is a four-generation pedigree with eight affected individuals (fig. 2). DNA is available from seven affected subjects, six at-risk subjects, and two unaffected spouses. Detailed clinical examination has been done in five affected subjects; one other subject experienced subjective unsteadiness, and a computed tomography (CT) scan showed moderate cerebellar atrophy. In the seventh affected member, no clinical details were available, but a family informant gave age-at-onset information. Male-to-male transmission was observed.

DNA Analysis

DNA was extracted from blood leukocytes with use of conventional methods. Affected subjects from both families do not have expansions in the SCA 1, 2, 3, 6, or 7 genes, and linkage of the disease to the SCA 4 (D16S422 and D16S289), SCA 5 (D11S903 and D11S905), and SCA 10 (D22S274) loci has been excluded (data not shown). To exclude point mutations in the SCA 6 gene, linkage to this locus was excluded with use of both the SCA 6 intronic marker D19S1105 and the polymorphic SCA 6 CAG repeat, which, although in the normal range, was sufficiently informative in these families (data not shown).

The Linkage Mapping Set Version 2 (Applied Biosystems) consists of ~400 fluorescently labeled primers that are used to amplify highly polymorphic chromosome-specific microsatellite markers, mostly from the Généthon map (Dib et al. 1996). PCR was done with the GeneAmp PCR system, with a total volume of 7.5 μl containing the following reagents: 10% PCR Buffer II, 2.5 mM $MgCl_2$, 0.25 mM each dNTP, 2.5 pmol each primer, 30 ng DNA, and 0.3 U AmpliTaq Gold. Samples were subjected to an initial denaturation step of 95°C for 12 min; followed by 10 cycles of 94°C for 15 s, 55°C for 15 s, and 72°C for 30 s; and then a further 20 cycles of 89°C for 15 s, 55°C for 15 s, and 72°C for 30 s. A final extension of 10 min at 72°C was specified. GeneAmp 9700 thermal cyclers were used.

Samples were run on 4% polyacrylamide gels with an ABI 377 automated sequencer equipped with GENESCAN (v. 3.1). Alleles were sized with GENOTYPER (v. 2.0).

Linkage Analysis and Haplotype Analysis

Using SLINK (Ott 1989; Weeks et al. 1990) with four alleles of equal frequency, we calculated maximum expected LOD scores for each family. For family 1, a maximum LOD score of 4.90 at recombination fraction (θ)=.00 was obtained, with an 80% chance of obtaining a LOD score > 3.0 For family 2, the maximum LOD score was 1.43 (θ = .00). For this reason, we have not undertaken a separate genome search in family 2.

Two-point LOD scores were computed for each marker with use of MLINK (Lathrop et al. 1984; Cottingham et al. 1993) of the FASTLINK (v. 3.0P) package. The disease was assumed to be autosomal dominant with a disease-allele frequency of .0001. Equal marker-allele frequencies were assumed. Only affected individuals and unaffected spouses were included in the linkage analysis. After the initial screen, we typed unaffected at-risk individuals to determine haplotypes but did not include them in the LOD-score calculations. Haplotypes were assigned manually, to insure that the smallest number of recombination events was inferred.

Results

Subjects

In family 1, mean age at onset was 24.7 ± 8.3 years (range 15–43 years, n = 17), and 37.6 ± 18.2 years (range 20–70 years, n = 7) in family 2. Statistically significant anticipation with respect to age at onset was not observed in family 1, in which mean ages at onset for generations IV–VII were 29.3 years (n = 3), 22 years (n = 5), 25.7 years (n = 7), and 24 years (n = 2), respectively. There was no significant difference between

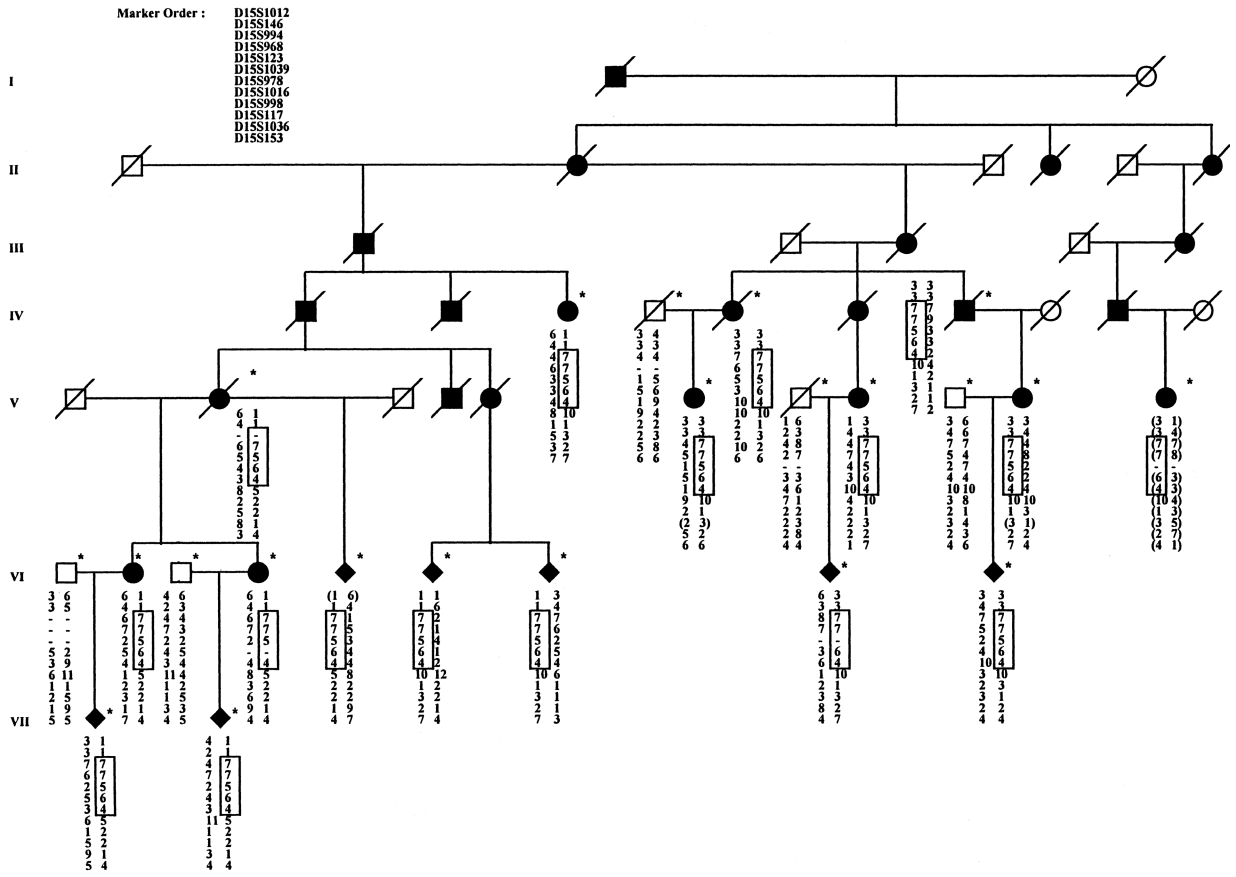

Figure 1 Abbreviated genealogical tree for family 1. Birth order has been changed and gender concealed in those individuals denoted by a diamond shape, to maintain the anonymity of the family. Unaffected at-risk individuals are not shown. Affected status is denoted by blackened symbols. An asterisk (*) denotes individuals for whom DNA samples are available. Haplotypes for chromosome 15 markers are shown; haplotypes cosegregating with the trait are boxed. Alleles in parenthesis are those for which phase could not be assigned with certainty. Dashes are used if the marker could not be typed. Informative recombination events place the SCA 11 disease locus between markers D15S146 and D15S1016.

these means (generation IV and V, $P = .34$; generation V and VI, $P = .50$; and generation VI and VII, $P = .68$). However, one subject, whose age at onset was 15 years, developed the disease before her mother who developed the disease at age 35 years. In family 2, evidence of anticipation could not be determined because of the small number of subjects.

The phenotype was similar in all affected subjects from both families and is that of a relatively "pure," slowly progressive, benign cerebellar syndrome, with no evidence of significant involvement of other central or peripheral nervous systems, consistent with ADCA III. Subjects in both families have normal life expectancy, with mean age at death 70.6 ± 13.7 years (range 55–88 years, $n = 8$) in family 1 and 74 ± 5.7 years (range 70–78 years, $n = 2$) in family 2. The major phenotypic features of both families are summarized and compared in table 2. Mild hyperreflexia (with negative Babinski sign) was found in all affected subjects from family 1 but in none from family 2. In addition, vertical nystagmus was present in 57% of affected members of family 1 but in none of family 2. The mean disease duration at examination in family 1 was 23.9 ± 13.4 years. No ophthalmoplegia, lower motor-neurone signs, or extrapyramidal features were observed in either family. Two affected subjects aged >75 years from family 2 had mild loss of deep sensation. No affected subjects in either family were wheelchair-bound.

Investigations

In family 1, nerve-conduction studies and electromyography were normal in three affected subjects. One other affected subject, aged 61 years (disease duration 29 years), had slightly small sensory action potentials (SAPs). Magnetic resonance imaging brain scans on three affected subjects showed isolated cerebellar atrophy. In family 2, a CT brain scan in one subject showed cerebellar atrophy. These results are characteristic of ADCA III.

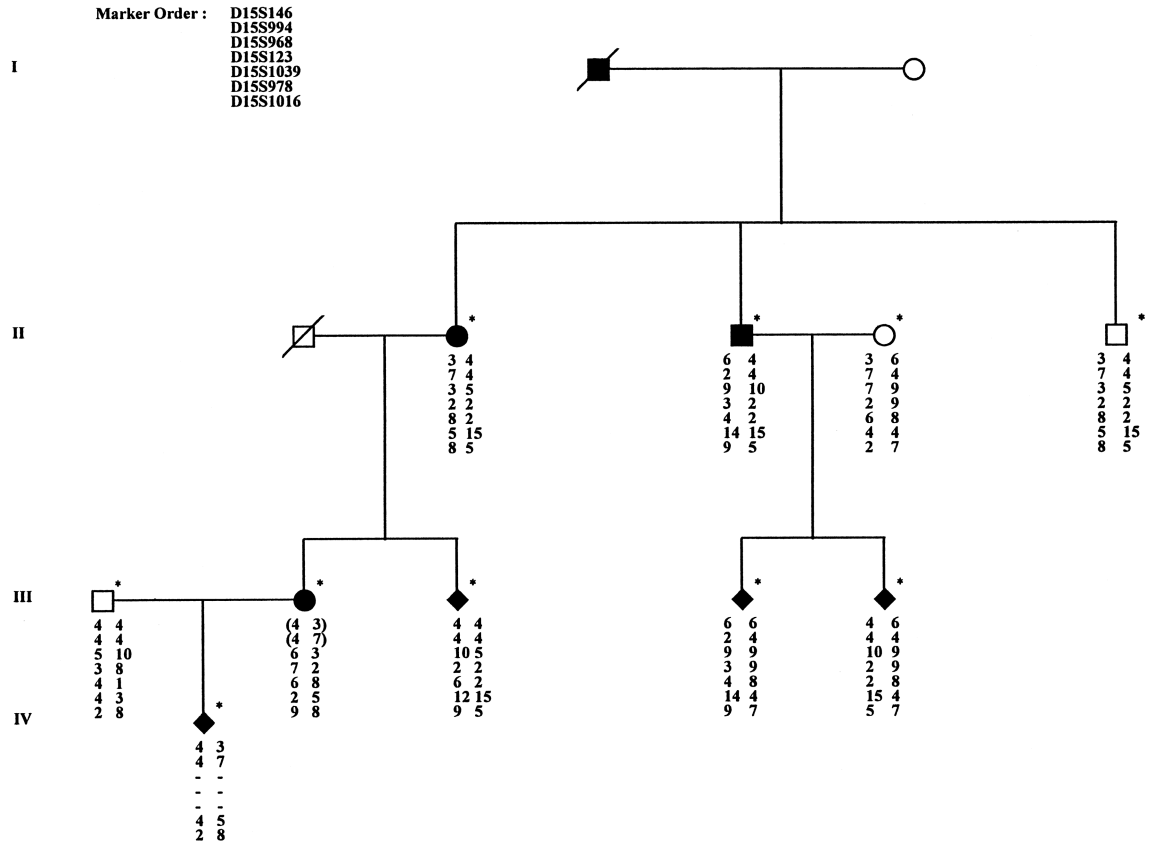

Figure 2 Abbreviated pedigree of family 2. Notation is the same as for figure 1. Affected individuals clearly have different haplotypes, thus excluding linkage of the disease to the SCA 11 locus in family 2.

Linkage Analysis (*Family 1*)

Microsatellite markers (350) were analyzed in family 1 before linkage to D15S994 and D15S978 was identified, with maximum LOD scores of 4.41 and 4.48, respectively, at $\theta = .00$. Additional markers in this region were then analyzed. Two-point LOD scores for family 1 are shown in table 3. A maximum LOD score of 4.67 ($\theta = .00$) was obtained with marker D15S1039. Small discrepancies exist between the various marker maps (Robinson et al. 1997), but the Généthon map places the markers in the following order: D15S1012-4.6 cM-D15S146-0.5 cM-D15S994-0.0 cM-D15S968-5.5 cM-D15S123-0.0 cM-D15S1039-0.0 cM-D15S978-1.6 cM-D15S1016-3.1 cM-D15S998-0.6 cM-D15S117-6.9 cM-D15S1036-4.4 cM-D15S153. Distances are sex-averaged.

Haplotype Analysis

Affected recombinants in family 1 place the locus within a 7.6-cM region on chromosome 15q14-21.3, between D15S146 and D15S1016 (fig. 1). This locus has been designated "SCA 11," after approval was given by the Human Genome Nomenclature Committee. A total of six unaffected at-risk individuals have been typed for the above markers, and five do not have the disease-associated haplotype (data not shown). Two of these subjects are 10 years older than the maximum age at onset observed in affected individuals, whereas the ages of the other three are within the age-at-onset range. Another unaffected subject, aged 34 years (i.e., within the age-at-onset range), carried the disease haplotype (data not shown), but this subject is not shown in figure 1, to maintain confidentiality. Moreover, these individuals do not help to define further the disease locus.

Linkage and Haplotype Analysis (*Family 2*)

Once linkage to the SCA 11 locus was established in family 1, individuals in family 2 were typed for the same markers. Two-point LOD scores are given in table 4. Figure 2 shows a haplotype analysis in family 2. Affected members have different haplotypes. Taken together, these data exclude linkage to the SCA 11 locus and provide evidence for a further ADCA III locus.

Table 2

A Comparison of the Clinical Features of Family 1 and 2

Clinical Feature	Family 1	Family 2
Disease duration (years) [a]	23.9 ± 13.4	...
Age at onset (years) [a]	24.7 ± 8.3	37.6 ± 18.2
	No. of Subjects (%)	
Gait ataxia	14 (100)	5 (100)
Eye movements:		
Jerky pursuit	14 (100)	5 (100)
Ophthalmoplegia[b]	0 (0)	0 (0)
Slow saccades	0 (0)	0 (0)
Limb ataxia	13 (93)	5 (100)
Dysarthria	14 (100)	4 (80)
Horizontal nystagmus	14 (100)	2 (40)
Hyperreflexia	14 (100)	0 (0)
Vertical nystagmus	8 (57)	0 (0)
Diplopia	1 (7)	1 (20)
Positive Babinski	0 (0)	0 (0)
Fasciculations	0 (0)	0 (0)
Loss of deep sensation	0 (0)	2 (40)[c]
Extrapyramidal signs	0 (0)	0 (0)

[a] Mean ± SD.
[b] Ophthalmoplegia includes both supranuclear and nuclear.
[c] Loss of deep sensation was very mild in these two individuals, both aged >75 years.

Discussion

Our data clearly establish the existence of two additional loci for ADCA III; one on chromosome 15q and another locus, which at present remains undefined. In family 1, we obtained a two-point LOD score of 4.67 with marker D15S1039 ($\theta = .00$). Haplotype analysis defined a 7.6-cM region between D15S146 and D15S1016 on 15q14-21.3. We genotyped a total of six unaffected at-risk individuals and found that five did not carry the disease-associated haplotype. Two of these subjects are >10 years older than the maximum age at onset observed in affected individuals, whereas the ages of the three other at-risk subjects were within the age-at-onset range. One unaffected subject, aged 34 years, had the disease haplotype. In family 2, we excluded linkage to markers D15S146–D15S1016, but this family is not large enough to define a new locus.

ADCA III is a relatively benign, slowly progressive, late-onset cerebellar syndrome, and the absence of involvement of other major systems (e.g., pyramidal, extrapyramidal, bulbar, or peripheral neuropathy) is characteristic (Harding et al. 1982, 1993). Three loci for ADCA III have been identified to date. A moderately expanded CAG repeat has been found in the SCA 6 gene on chromosome 19. This gene codes for the $\alpha_{1A}-$ subunit of the voltage-gated calcium channel (Zhuchenko et al. 1997) and results in an expanded polyglutamine tract in the C-terminal domain. This expansion has been shown to segregate with the disease phenotype in ~50% of ADCA III families investigated in this laboratory (P. Giunti, P. F. Worth, M. G. Sweeney, and N. W. Wood, unpublished data). The disease phenotype in a single family has been linked to the SCA 5 locus on chromosome 11 (Ranum et al. 1994), and Grewal et al. (1998) recently have described a family of Mexican descent with the clinical phenotype of ADCA III. Zu et al. (1999) subsequently have shown linkage of the disease in this family to a third ADCA III locus on chromosome 22q (SCA 10).

Although affected individuals in family 1 and 2 did not have an expansion in the SCA 6 gene, we excluded linkage to SCA 6 by using marker D19S1105 and the $(CAG)_n$ repeat in the SCA 6 gene to rule out point mutations at this locus. Point mutations in SCA 6 have been shown to account for families with episodic ataxia type 2, which may show a progressive ataxic phenotype (Zhuchenko et al. 1997).

The mean age at onset in family 1 was 24.7 ± 8.3

Table 3

Two-Point LOD Scores Between the SCA 11 Locus in Family 1 and Microsatellite Markers on Chromosome 15

	LOD Score at θ =							
Marker	.00	.001	.01	.05	.100	.200	.300	.400
D15S1012	−.81	.23	1.12	1.51	1.43	.98	.49	.15
D15S146	−.94	.09	.99	1.40	1.34	.95	.53	.21
D15S994	4.41	4.40	4.31	3.93	3.45	2.46	1.49	.65
D15S968	4.24	4.23	4.15	3.76	3.26	2.24	1.23	.40
D15S123	2.50	2.50	2.44	2.19	1.88	1.27	.72	.29
D15S1039	4.67	4.66	4.57	4.15	3.62	2.53	1.49	.62
D15S978	4.48	4.48	4.39	4.01	3.52	2.53	1.54	.67
D15S1016	.14	.13	.11	.44	.63	.61	.43	.21
D15S998	−5.76	−4.69	−2.82	−.99	−.37	.00	.06	.04
D15S117	−4.06	−2.75	−1.61	−.19	.28	.39	.24	.09
D15S1036	.46	1.51	2.39	2.71	2.54	1.87	1.10	.42
D15S153	−12.50	−8.91	−4.66	−1.50	−.40	.28	.33	.17

Table 4

Two-Point LOD Scores Between the ADCA III Locus in Family 2 and Microsatellite Markers on Chromosome 15

	LOD Score at θ =							
Marker	.00	.001	.01	.05	.1	.2	.3	.4
D15S146	−6.25	−4.41	−2.60	−1.26	−.72	−.24	−.04	.02
D15S994	−6.24	−4.39	−2.59	−1.25	−.71	−.24	−.04	.02
D15S968	−9.97	−6.95	−4.18	−2.16	−1.33	−.58	−.23	−.05
D15S123	−3.08	−2.35	−1.44	−.76	−.47	−.21	−.08	−.02
D15S1039	−6.26	−4.64	−2.87	−1.51	−.94	−.42	−.17	−.04
D15S978	−6.25	−4.33	−2.53	−1.20	−.66	−.20	−.01	.04
D15S1016	−6.28	−4.36	−2.57	−1.23	−.68	−.21	−.02	.04

years (range 15–43 years), which is considerably earlier than that of the series of SCA 6 expansion–positive subjects reported to date, with mean ages at onset having a range of 43–52 years (Geschwind et al. 1997; Matsumura et al. 1997; Matsuyama et al. 1997; Stevanin et al. 1997; Schöls et al. 1998; Yabe et al. 1998). However, it should be noted that the ranges overlap. The mean age at onset in family 2 was intermediate, between that of family 1 and that of SCA 6 (37.6 ± 18.2 years). These differing ages at onset are consistent with the observed genetic heterogeneity. The overall mean age at onset in the SCA 10 family was not given by the authors, but mean ages at onset for three successive generations were 42, 34.2, and 15.6 years, respectively (Grewal et al. 1998). Therefore, the overall mean age at onset in SCA 10 may also lie somewhere between that of SCA 6 and that of family 1. Life expectancy is not shortened in family 1 or 2 with mean ages at death of 70.6 ± 13.7 and 74 ± 5.7 years, respectively.

Family 1 and family 2 show the typical phenotype of ADCA III, which does not differ from that of SCA 6 CAG expansion–positive subjects or from that linked to SCA 10 (Grewal et al. 1998; Zu et al. 1999). A prominent cerebellar syndrome was common to all subjects, and the only noncerebellar signs observed were mild hyperreflexia (with a negative Babinski sign) and vertical nystagmus, in 57% of family 1. Therefore, clinical examination alone cannot reliably distinguish among the phenotypes of family 1, family 2, and SCA 6-positive ADCA III subjects. Investigations were as expected for ADCA III and revealed isolated cerebellar atrophy in three subjects from family 1 and in one from family 2. Neurophysiology showed small SAPs in one subject from family 1, aged 61 years, with disease duration of 29 years.

The phenomenon of anticipation is characteristic of most trinucleotide-repeat disorders except SCA 6, in which neither dramatic anticipation nor significant meiotic instability has been observed. The SCA 10 Mexican family reportedly exhibits anticipation with respect to age at onset, which has led researchers to suggest a trinucleotide repeat as the underlying pathogenic mechanism (Grewal et al. 1998; Zu et al. 1999). One individual in family 1 reported that she became affected before her mother, although statistically significant anticipation was not observed. Furthermore, there was no evidence of anticipation with respect to phenotypic severity. However, despite these observations, we cannot exclude the possibility that the mutational mechanism in the disease gene on chromosome 15q is a trinucleotide-repeat expansion, especially given the relatively small number of subjects.

In summary, these data more clearly define the genetic heterogeneity of ADCA III in accordance with that observed in ADCA I. Our analysis has defined a 7.6-cM region on chromosome 15 containing a novel ADCA III locus, designated SCA 11. This region of the genome spans >8 Mb, determined on the basis of the physical map of the region, with ~80% covered by existing YACs. However, this region is not well defined, and the lack of consensus between the marker maps suggests that this estimate may not be particularly accurate. A large number of ESTs (>50) and known genes have been mapped to this region, but none of those identified represents an obvious candidate for SCA 11. A further refinement of the locus in conjunction with physical-mapping studies, possibly aided by the repeat-expansion–detection method (Schalling et al. 1993) could enable us to identify this novel ADCA III locus.

Acknowledgments

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Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for SCA 1 [MIM 164400], 2 [MIM 183090], 3 [MIM 109150], 5 [MIM 600224], 6 [MIM 183086], and 10 [MIM 603516]; and for ADCA II [MIM 164500] and III [MIM 117210])

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