Am. J. Hum. Genet. 56:193–201, 1995

The Gene for Spinal Cerebellar Ataxia 3 (SCA3) Is Located in a Region of ~3 cM on Chromosome 14q24.3-q32.2

Giovanni Stevanin,[1] Géraldine Cancel,[1] Alexandra Dürr,[1] Hervé Chneiweiss,[2] Odile Dubourg,[1] Jean Weissenbach,[3] Howard M. Cann,[4] Yves Agid,[1] and Alexis Brice[1]

[1]Inserm U289, Hôpital de la Salpêtrière, [2]Inserm U114, Collège de France, and [3]Fondation Jean Dausset–CEPH, Paris; and [4]Généthon, Evry

Summary

SCA3, the gene for spinal cerebellar ataxia 3, was recently mapped to a 15-cM interval between D14S67 and D14S81 on chromosome 14q, by linkage analysis in two families of French ancestry. The SCA3 candidate region has now been refined by linkage analysis with four new microsatellite markers (D14S256, D14S291, D14S280, and AFM343vf1) in the same two families, in which 19 additional individuals were genotyped, and in a third French family. Combined two-point linkage analyses show that the new markers, D14S280 and AFM343vf1, are tightly linked to the SCA3 locus, with maximal lod scores, at recombination fraction, (θ)=.00, of 7.05 and 13.70, respectively. Combined multipoint and recombinant haplotype analyses localize the SCA3 locus to a 3-cM interval flanked by D14S291 and D14S81. The same allele for D14S280 segregates with the disease locus in the three kindreds. This allele is frequent in the French population, however, and linkage disequilibrium is not clearly established. The SCA3 locus remains within the 29-cM region on 14q24.3-q32.2 containing the gene for the Machado-Joseph disease, which is clinically related to the phenotype determined by SCA3, but it cannot yet be concluded that both diseases result from alterations of the same gene.

Introduction

The type I autosomal dominant cerebellar ataxias (ADCA) are a hereditary group of neurological disorders, characterized by degeneration of the cerebellum, spinal cord, and brainstem (Harding 1993). It is widely accepted that the type I ADCAs are clinically heterogeneous, since patients present, in addition to progressive cerebellar ataxia, various combinations of other neurological signs and symptoms, such as pyramidal and extrapyramidal signs, deep sensory loss, ophthalmoplegia, and dementia (Dürr et al. 1993; Harding 1993). Clinical heterogeneity is found both within and among families and has recently been shown to be related to disease duration (Dürr et al. 1993).

Genetic heterogeneity also complicates classification of ADCA type I. At least four different loci have been identified: SCA1, on chromosome 6p23.05-p24 (Yakura et al. 1974; Ranum et al. 1991; Zoghbi et al. 1991; Volz et al. 1992; Khati et al. 1993), SCA2, on chromosome 12q23-q24.1 (Gispert et al. 1993; Pulst et al. 1993; Belal et al. 1994), SCA3, on chromosome 14q24.3-qter (Stevanin et al. 1994), and SCA4, on chromosome 16q24-qter (Gardner et al. 1994). A locus that includes the SCA3 candidate region has also been reported for Machado-Joseph disease (MJD) (Takiyama et al. 1993), a form of ADCA type I (Harding 1993). Linkage analysis of SCA3 families with markers linked to MJD could not distinguish the locations of the genes determining the two diseases (Stevanin et al. 1994).

The present study was undertaken to refine the genetic localization of SCA3. Linkage analysis was performed in three French families, with four newly developed microsatellite markers situated within the previously defined 15-cM candidate region for SCA3, between D14S67 and D14S81. Combined linkage and recombinant haplotype analyses have now reduced this region to 3 cM.

Subjects and Methods

Subjects

Three unrelated Caucasian families (SAL-305, SAL-339, and SAL-358) originating from different regions in France and presenting with ADCA type I, according to the diagnostic criteria described elsewhere (Dürr et al. 1993; Khati et al. 1993; Stevanin et al. 1994), were studied. One hundred eight consenting members were examined, 27 of whom were affected (table 1). Individual SAL-305-47, who presented with moderate cerebellar ataxia and subtle dysarthria, insufficient for a definite diagnosis of ADCA type I, was considered to be diagnostically unknown for linkage analysis, except when otherwise indicated. Male-to-male transmission was observed in the three kindreds, excluding X-linked inheritance. Blood samples were taken from all

Received May 31, 1994; accepted for publication October 3, 1994.

Address for correspondence and reprints: Dr. Giovanni Stevanin, INSERM U 289, Hôpital de la Salpêtrière, 47 Boulevard de l'Hôpital 75651 Paris Cédex 13, France.

0002-9297/95/5601-0025$02.00

Table 1

Families Studied

Family	Mean Age at Disease Onset ± SD (range) (years)	Sampled Individuals			
		Affected	At Risk	Married-in	Total
SAL-305	31 ± 6 (20–40)	10	14[a]	6	30
SAL-339	40 ± 12 (30–62)	8	12	5	25
SAL-358	34 ± 8 (17–47)	9	36	8	53
Overall	34 ± 9 (17–62)	27	62	19	108

[a] Including an individual who is diagnostically unknown.

examined individuals, and critical recombinants were confirmed with DNA from two independent samples. High-molecular-weight DNA was purified, using a simplified procedure (Miller et al. 1988). Permanent lymphoblastoid cell lines were established for affected individuals by transformation with the Epstein-Barr virus (Neitzel 1986).

The SCA3 locus has already been assigned to chromosome 14q24.3-qter by linkage analysis in families SAL-305 and SAL-358 (Stevanin et al. 1994). Nineteen additional subjects from these families, two of whom were affected, were also included in the present study. In addition, linkage to the SCA1 (Khati et al. 1993) and SCA2 (Cancel et al., in press) loci has been excluded in family SAL-339.

Markers

The newly sampled individuals were genotyped for markers D14S55, D14S48 (Takiyama et al. 1993), D14S67, D14S81, and D14S62 (Weissenbach et al. 1992). All subjects in the three families were genotyped for four new microsatellite markers developed at Généthon: D14S256, D14S291, D14S280 (Gyapay et al. 1994), and AFM343vf1. Primer sequences were 5′-GCATTTTGGAGAATACATTTGG-3′ and 5′-GCTGTCNAATAAAATATATCCAACA-3′, for D14S256; 5′-ACCAGGCTTCATGCCA-3′ and 5′-CTCTACGCTAGTGACTTTCAGG-3′, for D14S291; 5′-GGGCAACAGAGCAGATTTC-3′ and 5′-GCACCCAGGCCAGAAC-3′, for D14S280; and 5′-CCTGGGGCAAGGTAAG-3′ and 5′-GGGGGGACATTGTGAG-3′, for AFM343vf1.

Genotyping

Each microsatellite was amplified by PCR under standard conditions (Stevanin et al. 1994). Genotypes were determined after electrophoresis on denaturing acrylamide gels, blotting onto charged nylon membranes, hybridization with a $5'\gamma P^{32}$ labeled primer from each pair, and autoradiography (Stevanin et al. 1994). To avoid experimental errors, all individuals were typed at least twice, and individuals in whom a recombination was observed were sampled a second time.

Linkage Analysis

The relative positions of the markers D14S256, D14S280, D14S291, and AFM343vf1, with respect to previously mapped 14q markers, were determined with genotypes from the CEPH database for at least eight CEPH families, using the CLODSCORE and CILINK options of LINKAGE (Lathrop and Lalouel 1991). Markers D14S45, D14S48, and D14S55 had been genotyped in all or most informative reference families. The most likely order is presented in figure 1. This order is supported by odds of 344:1 against the next most likely order, which differs from the former by the inversion of D14S55 and D14S73,

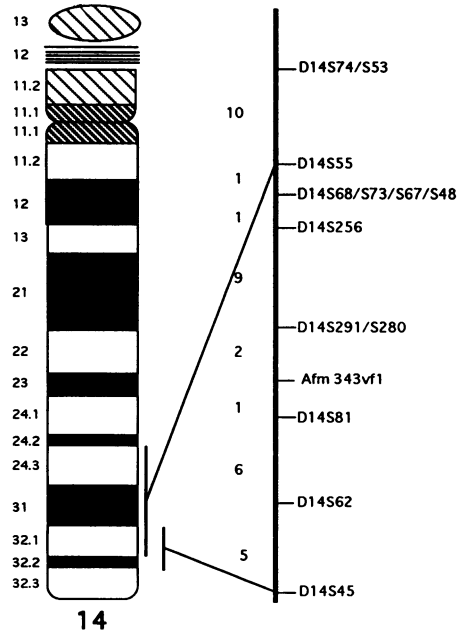


Figure 1 Physical and regional CEPH (sex-averaged) genetic map of chromosome 14q. D14S55, the most centromeric locus on the map, is localized to 14q24.3-q32.1. D14S45, the most telomeric marker on the map, is localized to 14q32.1-q32.2. These cytogenetic localizations were obtained from the Genome Data Base, Baltimore.

Table 2

Allele Frequencies for Nine Chromosome 14q Markers in the French Population

	MARKER[b]								
ALLELES[a]	D14S55 (66)	D14S48 (66)	D14S67 (100)	D14S256 (66)	D14S291 (52)	D14S280 (100)	AFM343vf1 (72)	D14S81 (92)	D14S62 (82)
0	...	.015[c]	.002[d]	...	.018[e]	...	...	.054[f]	...
1	.030[g]	.000	.010	.030[h]	.242	.010[i]	.097[j]	.054	.049[k]
2	.136	.197	.060	.015	.685	.020	.180	.066	.330
3	.682	.015	.160	.015	.000	.210	.083	.119	.158
4	.122	.288	.210	.015	.055	.120	.140	.380	.049
5	.030	.000	.070	.015	...	.520	.069	.044	.000
6	...	.121	.090	.015	...	.090	.042	.109	.158
7	...	.030	.140	.181	...	.020	.389	.044	.012
8	...	.273	.080	.000	...	.010	...	.130	.012
9	...	.061	.050	.030	...	...	...	...	.000
10	...	...	.010	.015	...	...	...	...	.220
11	...	...	.010	.015	...	...	...	...	.000
12	...	...	.007	.270	...	...	...	...	.012
13	...	...	.000	.378	...	...	...	...	...
14	...	...	.020	.000	...	...	...	...	...
15	...	...	...	.015	...	...	...	...	...

[a] Alleles are numbered such that the longest allele is assigned the lowest number and each successive allele is 2 bp smaller, except for marker D14S62 (1 bp smaller).

[b] Numbers in parentheses represent number of chromosomes tested for each marker.

[c] 277 bp

[d] 157 bp

[e] 218 bp

[f] 191 bp

[g] 130 bp

[h] 150 bp

[i] 243 bp

[j] 139 bp

[k] 129 bp

located ~10 cM proximal to the candidate region. The odds against all other orders generated by inversion of adjacent locus pairs or by testing AFM343vf1 in each interval of the most likely map were $\geq 5.9\times10^3$:1. D14S280 was placed on the map at the same location as D14S291, because pairwise linkage analysis showed no recombination between these loci (maximum lod score [Z_{max}] of 17.0). The genetic location of AFM343vf1, between D14S291 and D14S81, is supported by odds of $\geq 7.4\times10^4$:1 against all other positions on the map.

Linkage analyses of SCA3 families were performed, using the MLINK and LINKMAP programs of the computer package LINKAGE version 5.1 (Lathrop and Lalouel 1991). Penetrance of the disease was taken into account by assigning subjects to one of five liability classes determined according to the method of Ott (1991), from the cumulative age at onset (AAO) curve of the three families. For patients >59 years of age, maximal penetrance was set at 96%. A disease frequency of .0001 and equal recombination fractions (θ) between males and females were assumed. Allele frequencies at each locus were determined in unrelated French subjects (table 2). Multipoint analysis was performed, taking into account the sex-averaged intermarker recombination rates indicated in figure 1. Alleles at each marker locus were recoded to minimize the number, without loss of linkage information. Alleles that were transmitted from the unaffected parent or that were not observed in patients were pooled and considered as a single allele. The frequency used for the allele segregating with the disease locus was always its calculated value.

Results

Pairwise Linkage Analyses

One hundred eight individuals from three ADCA type I families (table 1), originating from different regions in France, were genotyped for four new microsatellite markers—D14S256, D14S291, D14S280 (Gyapay et al. 1994), and AFM343vf1—recently developed at Généthon (fig. 1). In addition, individuals from family SAL-339 and newly

Table 3

Pairwise Z Values for SCA3 and Nine 14q Microsatellites in Three Kindreds

Marker	Family	Z at θ = .00	.01	.05	.10	.20	.30	.40	Z_{max}	θ_{max}
D14S55	SAL-305	2.34	2.30	2.11	1.86	1.32	.75	.24	2.34	.00
	SAL-339	−3.88	−.35	.26	.45	.48	.33	.14	.49	.16
	SAL-358	−11.04	−2.39	−.34	.40	.80	.66	.27	.81	.21
	Overall	−12.58	−.44	2.03	2.71	2.60	1.74	.65	2.80	.13
D14S48	SAL-305	−8.16	−1.25	.00	.40	.55	.42	.20	.55	.18
	SAL-339	−3.36	−.01	.55	.66	.58	.36	.14	.67	.11
	SAL-358	−10.98	−1.43	.42	.99	1.16	.84	.33	1.18	.17
	Overall	−22.50	−2.69	.97	2.05	2.29	1.62	.67	2.36	.14
D14S67	SAL-305	−.10	3.35	3.69	3.51	2.79	1.84	.77	3.69	.05
	SAL-339	−.96	2.38	2.78	2.70	2.16	1.43	.60	2.79	.06
	SAL-358	−16.25	−.75	1.08	1.62	1.70	1.26	.55	1.75	.16
	Overall	−17.31	4.98	7.55	7.83	6.65	4.53	1.92	7.85	.08
D14S256	SAL-305	.39	.39	.37	.35	.28	.19	.10	.39	.00
	SAL-339	−.85	2.48	2.89	2.82	2.30	1.57	.70	2.90	.06
	SAL-358	−13.93	−.99	.86	1.43	1.55	1.17	.51	1.59	.16
	Overall	−14.39	1.88	4.12	4.60	4.13	2.93	1.31	4.60	.11
D14S291	SAL-305	.71	.70	.66	.60	.47	.33	.17	.71	.00
	SAL-339	−2.92	.36	.83	.84	.54	.17	.00	.87	.07
	SAL-358	.30	.32	.37	.41	.42	.31	.11	.43	.15
	Overall	−1.91	1.38	1.86	1.85	1.43	.81	.28	1.89	.07
D14S280	SAL-305	1.77	1.74	1.61	1.44	1.07	.70	.34	1.77	.00
	SAL-339	2.63	2.55	2.24	1.83	.96	.19	−.07	2.63	.00
	SAL-358	2.65	2.61	2.42	2.17	1.61	.99	.35	2.65	.00
	Overall	7.05	6.90	6.27	5.44	3.64	1.88	.62	7.05	.00
AFM343vf1	SAL-305	6.33	6.23	5.80	5.23	4.01	2.67	1.21	6.33	.00
	SAL-339	2.33	2.29	2.12	1.90	1.43	.91	.37	2.33	.00
	SAL-358	5.04	4.95	4.59	4.11	3.09	1.97	.82	5.04	.00
	Overall	13.70	13.47	12.51	11.24	8.53	5.55	2.40	13.70	.00
D14S81	SAL-305	−2.50	.77	1.26	1.30	1.07	.72	.35	1.31	.08
	SAL-339	−3.50	2.28	2.70	2.63	2.12	1.40	.57	2.70	.06
	SAL-358	1.89	1.88	1.85	1.75	1.42	.92	.34	1.89	.00
	Overall	−4.11	4.93	5.81	5.68	4.61	3.04	1.26	5.82	.06
D14S62	SAL-305	−8.47	−2.31	−.41	.25	.61	.52	.24	.61	.22
	SAL-339	−5.03	−.07	.47	.58	.47	.25	.07	.58	.11
	SAL-358	−3.41	2.40	2.82	2.74	2.20	1.43	.56	2.83	.06
	Overall	−16.91	.02	2.88	3.57	3.28	2.20	.87	3.62	.12

included members of families SAL-305 and SAL-358 were genotyped with markers D14S62, D14S81, D14S67, D14S48, and D14S55. The other subjects in families SAL-305 and SAL-358 had already been genotyped for these five markers. The results of pairwise linkage analysis of SCA3 with each of the nine loci that are localized to the candidate region are presented in table 3. For the three families combined, Z_{max} values exceeded the threshold (3.0) for detection of linkage of SCA3 to loci D14S67, D14S81, D14S62, D14S256, AFM343vf1, and D14S280. Recombination occurred between SCA3 and each of the first four of these loci. The combined Z_{max} values were 7.05 and 13.70, both at maximum θ (θ_{max}) of .00, for D14S280 and AFM343vf1, respectively. Thus, recombination was not found between SCA3 and either AFM343vf1 or D14S280. With markers that were less informative in the SCA3 families (i.e., D14S55, D14S48 and D14S291), combined z values were positive but did not reach 3.0.

Multipoint Linkage Analyses

Multipoint linkage analysis was carried out separately for each of the three families to situate the disease locus relative to markers D14S291, AFM343vf1, and D14S81. Multipoint Z_{max} values of 6.47, 4.56, and 5.35 were obtained at AFM343vf1 for families SAL-305, SAL-339, and SAL-358, respectively (data not shown). The result of

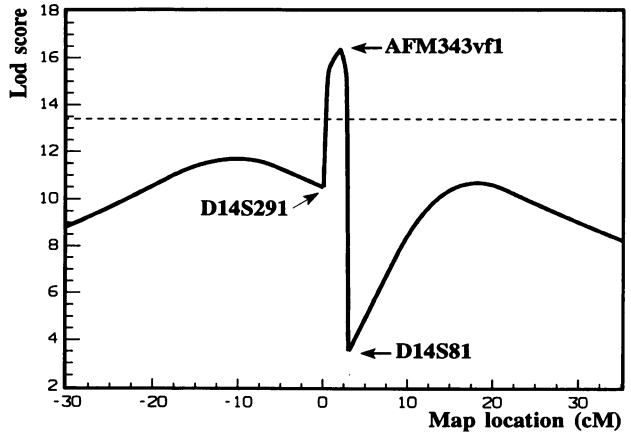


Figure 2 Combined-multipoint linkage analysis of families SAL-305, SAL-339, and SAL-358. The genetic locations of the markers used are indicated on the x-axis. The dotted line represents the (Z_{max-3}) confidence interval.

multipoint analysis for the three families combined is shown in figure 2. The most likely location of SCA3 was found to be at AFM343vf1 (multipoint Z_{max} value of 16.40). The Z_{max-3} confidence interval (1,000:1 odds) restricted SCA3 to a 3-cM region, between D14S291 and D14S81. Two other Z_{max} values were observed, ~12 cM centromeric to D14S291 and ~15 cM telomeric to D14S81, but the odds against these locations were >1,000:1 (fig. 2).

Analysis of Recombinant Haplotypes

Haplotypes at eight marker loci, spanning ~20 cM, including the candidate region, were determined in the three families segregating SCA3 (fig. 3). Recombination events were consistent with the genetic map. In the case of markers D14S291 and D14S280, which did not recombine in eight CEPH reference families (Gyapay et al. 1994), a single confirmed recombinant haplotype carried by patient SAL-339-19 established their order. This position was confirmed by a recombination transmitted from individual SAL-358-21, unaffected and not at risk, to individual SAL-358-61. The segregating haplotypes are indicated on partial pedigrees in figure 3.

There was no evidence of recombination, in any of the kindreds, between SCA3 and either AFM343vf1 or D14S280, confirming the linkage analysis. Recombinations involving proximal or distal markers restricted SCA3 to the 3-cM interval between D14S291 and D14S81 (fig. 3). D14S291 was established as the centromeric boundary by a recombination event between it and SCA3, an event observed in individual SAL-339-19 and transmitted to his unaffected daughter (SAL-339-39). This limit was supported by more proximal recombination events observed in individuals SAL-358-35, -47, and -60, in whom SCA3 segregated with D14S291 and the more distal markers. The recombinant haplotype carried by individual SAL-358-35 was transmitted to her affected daughter (SAL-358-92). The telomeric boundary of the candidate region was placed at D14S81 by a recombination, between it and SCA3, AFM343vf1, and more proximal loci, that probably occurred in individual SAL-305-23. The resulting recombinant haplotype was then transmitted from SAL-305-30 to SAL-305-55 and to SAL-305-58, in whom it was observed, as well as to SAL-305-57, who, in turn, transmitted it to her affected daughter (SAL-305-75). This distal boundary was confirmed by an independent recombination event detected in individual SAL-339-30.

Individuals SAL-339-39 and SAL-358-59 have inherited the disease-bearing chromosome but are still unaffected at the ages of 31 and 39 years, respectively. Since penetrance for this age class does not exceed 40%, the absence of symptoms is not surprising.

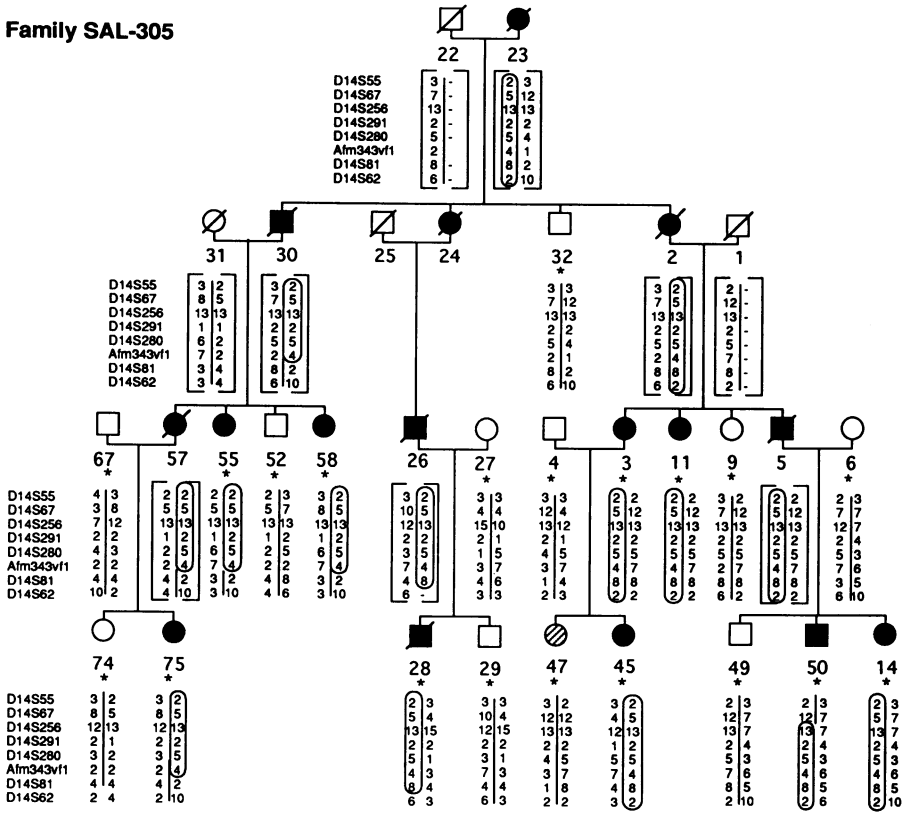
Consistent with the results of multipoint linkage analyses, the most likely location for SCA3 was therefore between D14S291 and D14S81. Within this interval, the same D14S280 allele (allele 5) segregated with SCA3 in all three families. Allele 2 of D14S291 was also found in all affected members of the three kindreds, except SAL-339-19, in whom a recombination between this marker and SCA3 was observed. Each of these alleles is most frequent in the French population (table 2), probably accounting for the absence of significant linkage disequilibrium between SCA3 and each of these two marker loci.

Discussion

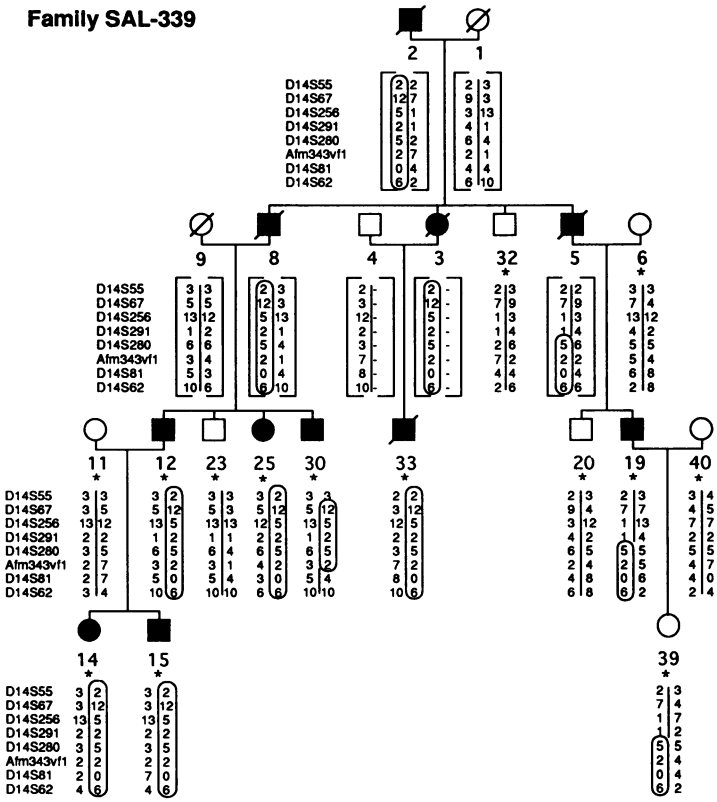
The present study, combining linkage and haplotype analyses of three families originating from different regions in France, confirms that SCA3 maps to 14q24.3-q32.2 and establishes its position, in a 3-cM interval between D14S291 and D14S81, in which it is tightly linked to both AFM343vf1 and D14S280; no recombinations were observed with these markers. Although the same D14S280 allele segregated with SCA3 in the three families, linkage disequilibrium could not be demonstrated, because this allele is frequent, and additional families need to be studied.

Individual SAL-305-47, 32 years of age at the time of her clinical examination, presented with moderate cerebellar ataxia, subtle dysarthria, and brisk tendon reflexes. These clinical signs, though suggestive, are insufficient to diagnose ADCA type I. An unrelated neurological disorder cannot be formally excluded. The patient did not consent to further investigations, including cerebral computerized tomography scan. If this individual indeed carries SCA3, a recombination would have occurred between SCA3 and AFM343vf1, located within the 3-cM candidate interval. Unfortunately, the boundary of the recombination event

Family SAL-305



Family SAL-339



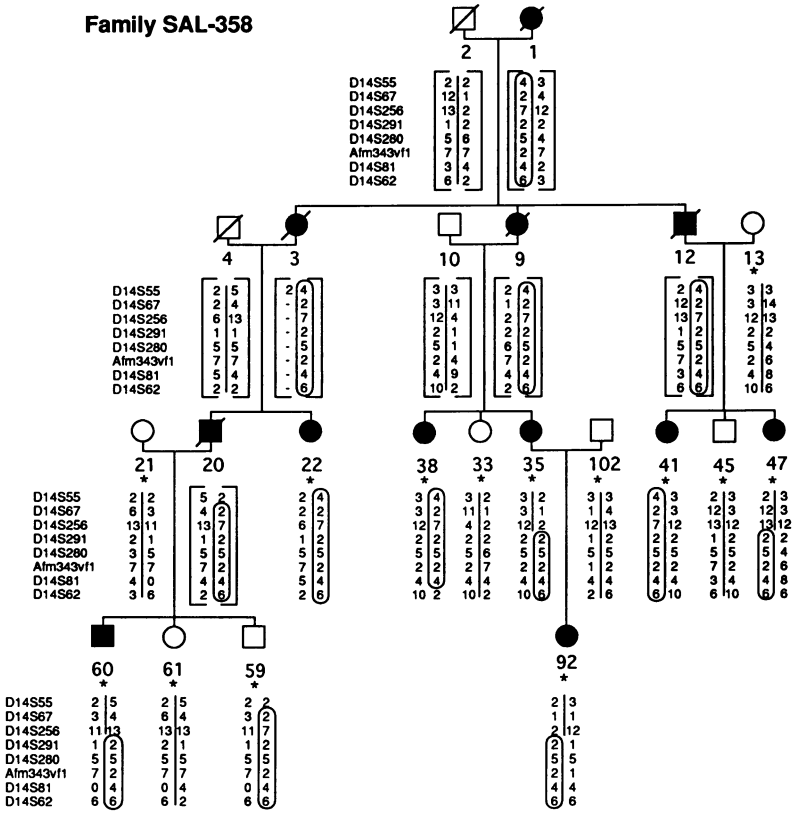


Figure 3 Haplotypes in families SAL-305, SAL-339, and SAL-358, for eight chromosome 14q markers. Each individual is identified by the local identification number. An asterisk (*) indicates subjects who were sampled. The hatched symbol indicates an individual of unknown diagnostic status. Haplotypes segregating with the disease are circled, and inferred haplotypes are bracketed. Only partial pedigrees are shown, and reconstructed haplotypes are supported by analysis of other individuals not represented in the figure. D14S291 and D14S280 were positioned by haplotyping, in the present study.

cannot be determined, because of the homozygosity of the affected mother (SAL-305-3) at six of eight haplotype loci.

The clinical characteristics of the three SCA3 families studied are similar to those of other ADCA type I patients in previous reports (Dürr et al. 1993; Khati et al. 1993; Stevanin et al. 1994). The age at onset in family SAL-339 is, however, significantly greater than in the other two SCA3 families studied here (table 1, $P<.05$). The clinical features of the disease are variable, however, even within families, and overlap with those of other autosomal dominant diseases presenting cerebellar ataxia, in particular Machado-Joseph disease (MJD) (Harding 1993) and the ataxo-choreic form of dentato-rubro-pallido-luysian atrophy (DRPLA) (Iizukza et al. 1984). MJD differs clinically from SCA3 by the higher frequency of dystonia and facio-lingual myokymia (Stevanin et al. 1994). The MJD gene has been mapped, however, to the 14q region containing the SCA3 locus (Takiyama et al. 1993). Although SCA3 is $\geq$10 cM from the markers that are closely linked to MJD (markers D14S55 and D14S48), the present study was unable to determine whether the same or two different loci are implicated in these disorders. A more precise localization of the 14q MJD gene is necessary. Finally, a gene segregating with neuropathologically confirmed DRPLA may also be localized to the 14q region containing the gene(s) for SCA3 and MJD (Cancel et al. 1994), in a family where the (CAG)n sequence of the DRPLA gene located on chromosome 12p (Koide et al 1994; Nagafuchi et al. 1994) is not implicated (O. Dubourg, A. Dürr, G. Cancel, G. Stevanin, H. Y. Zoghbi, and H. T. Orr, unpublished data). Conversely, Warner et al. (1994) have described a family with the unstable CAG of the DRPLA locus on chromosome 12p that does not show the neuropathological signs of DRPLA. Thus, the molecular origin of these diseases cannot be deduced from clinical or neuropathological observations.

The defects in SCA1 (Chung et al. 1993; Matilla et al. 1993; Orr et al. 1993; Giunti et al. 1994; Dubourg et al., in press) and the DRPLA gene localized to chromosome 12p (Koide et al., 1994; Nagafuchi et al. 1994) are known to be expanded unstable triplet repeat sequences (CAG) that result in anticipation. Anticipation has also been reported

to occur in SCA2 (Pulst et al. 1993; Belal et al. 1994) and other ADCA type I kindreds (Dürr et al. 1993). Unstable, expanded trinucleotide repeats may be the genetic defect in the SCA3 and MJD genes, as well. If this were the case, the phenotypic differences between these two diseases would be difficult to explain. Different alleles at the same locus might, however, be involved.

The present study has considerably reduced the interval known to contain SCA3, facilitating the isolation of this gene by positional cloning. It has also provided informative, closely linked markers for testing linkage to the SCA3 locus, markers that could be used to detect linkage disequilibrium and to develop an accurate presymptomatic diagnostic test.

Acknowledgments

The authors thank Drs. Merle Ruberg and Eric LeGuern for helpful discussion and critical reading of the manuscript. We are grateful to Christiane Penet, Isabelle Lagroua, Yolaine Pothin, Alain Ploska, and Françoise Rogerieux for technical assistance. The logistic and technical support of Généthon is acknowledged, particularly the contribution of Drs. Sophie Marc and Alain Vignal, Claire Bichat and Sylvie Duveirneuil. We especially thank the families for their participation in this study, and Dr. Bernard Ducamp and Profs. Michel Haguenau and Gérald Rancurel for referring some of the index patients. This work was supported by the Association Française contre les Myopathies (AFM), the Institut National de la Santé et de la Recherche Médicale, the Groupement de Recherches et d'Études sur les Génomes, the Verum Foundation, and the Association pour le Développement de la Recherche sur les Maladies Génétiques Neurologiques et Psychiatriques. G.S. is a recipient of a fellowship from the AFM and O.D. is a recipient of a fellowship from the Fondation pour la Recherche Médicale.

References

Belal S, Cancel G, Stevanin G, Hentati F, Khati C, BenHamida C, Auburger G, et al (1994) Clinical and genetic analysis of a Tunisian family with autosomal dominant cerebellar ataxia type I linked to the SCA2 locus. Neurology 44:1423-1426

Cancel G, Dürr A, Stevanin G, Chneiweiss H, Duyckaerts C, Serdaru M, deToffol B, et al (1994) Is DRPLA also linked to 14q? Nature Genet 6:8

Cancel G, Stevanin G, Dürr A, Chneiweiss H, Penet C, Pothin Y, Agid Y, et al. SCA2 is not a major locus for ADCA type I in French families. Am J Med Genet (in press)

Chung M-Y, Ranum LPW, Duvick LA, Servadio A, Zoghbi HY, Orr HT (1993) Evidence for a mechanism predisposing to intergenerational CAG repeat instability in spinocerebellar ataxia type I. Nature Genet 5:254–258

Dubourg O, Dürr A, Cancel G, Stevanin G, Chneiweiss H, Penet C, Agid Y, et al. Analysis of the SCA1 CAG repeat in a large number of families with dominant ataxia: clinical and molecular correlations. Ann Neurol (in press)

Dürr A, Chneiweiss H, Khati C, Stevanin G, Cancel G, Feingold J, Agid Y, et al (1993) Phenotypic variability in autosomal dominant cerebellar ataxia type I is unrelated to genetic heterogeneity. Brain 116:1497–1508

Gardner K, Alderson K, Galster B, Kaplan C, Leppert M, Ptacek L (1994) Autosomal dominant spinocerebellar ataxia: clinical description of a distinct hereditary ataxia and genetic localization to chromosome 16 (SCA4) in a Utah kindred. Neurology Suppl 44:921

Gispert S, Twells R, Orozco G, Brice A, Weber J, Heredero L, Scheufler K, et al (1993) Chromosomal assignment of the second (cuban) locus for autosomal dominant cerebellar ataxia (SCA2) to human chromosome 12q23-24.1. Nature Genet 4: 295–299

Giunti P, Sweeney MG, Spadaro M, Jodice C, Novelletto A, Malaspina P, Frontali M, et al. (1994) The trinucleotide repeat expansion on chromosome 6p (SCA1) in autosomal dominant cerebellar ataxias. Brain 117:645–649

Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, et al (1994) An intermediary report on the Généthon human linkage map. Nature Genet 7:246–339

Harding AE (1993) Clinical features and classification of inherited ataxias. In: Harding AE, Deufel T (eds) Inherited ataxias. Vol 61 in: Advances in neurology. Raven, New York, pp 1–14

Iizukza R, Hirayama K, Maehara K (1984) Dentatorubro-pallidoluysian atrophy: a clinico-pathological study. J Neurol Neurosurg Psychiatry 47:1288–1298

Khati C, Stevanin G, Durr A, Chneiweiss H, Belal S, Seck A, Cann H, et al (1993) Genetic heterogeneity of autosomal dominant cerebellar ataxia type I: clinical and genetic analysis of ten French families. Neurology 43:1131–1137

Koide R, Ikeuchi T, Onodera O, Tanaka H, Igarashi S, Endo K, Takahashi H, et al (1994) Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Nature Genet 6:9–13

Lathrop GM, Lalouel JM (1991) Statistical methods for linkage analysis. In: Rao CR, Chakraborty R (eds) Handbook of statistics, Vol 8. Elsevier, Amsterdam, pp 81–123

Matilla T, Volpini V, Genis D, Rosell J, Corral J, Dàvalos A, Molins A, et al (1993) Presymptomatic analysis of spinocerebellar ataxia type 1 (SCA1) via the expansion of the SCA1 CAG-repeat in a large pedigree displaying anticipation and parental male bias. Hum Mol Genet 2:2123–2128

Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16:1215

Nagafuchi S, Yanagisawa H, Sato K, Shirayama T, Ohsaki E, Bundo M, Takeda T, et al (1994) Dentatorubral and pallidoluysian atrophy expansion of an unstable CAG trinucleotide on chromosome 12p. Nature Genet 6:14–18

Neitzel H (1986) A routine method for the establishment of permanent growing lymphoblastoid cell lines. Hum Genet 73: 320–326

Orr HT, Chung M-Y, Banfi S, Kwiatkowski TJ Jr, Servadio A, Beaudet AL, McCall AE, et al (1993) Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nature Genet 4:221–226

Ott J (ed) (1991) Analysis of human genetic linkage, 2d ed. Johns Hopkins University Press, Baltimore

Pulst SM, Nechiporuk A, Starkman S (1993) Anticipation in spinocerebellar ataxia type 2. Nature Genet 5:8–10

Ranum LPW, Duvick LA, Rich SS, Schut LJ, Litt M, Orr HT (1991) Localization of the autosomal dominant HLA-linked spinocerebellar ataxia (SCA1) locus, in two kindreds, within an 8-cM subregion of chromosome 6p. Am J Hum Genet 49:31–41

Stevanin G, Le Guern E, Ravisé N, Chneiweiss H, Dürr A, Cancel G, Vignal A, et al (1994) A third locus for autosomal dominant cerebellar ataxia type I maps to chromosome 14q24.3-qter: evidence for the existence of a fourth locus. Am J Hum Genet 54:11–20

Takiyama Y, Nishizawa M, Tanaka H, Kawashima S, Sakamoto H, Karube Y, Shimazaki H, et al (1993) The gene for Machado-Joseph disease maps to human chromosome 14q. Nature Genet 4:300–304

Volz A, Fonatsch C, Ziegler A (1992) Regional mapping of the gene for autosomal dominant spinocerebellar ataxia (SCA1) by localizing the closely linked D6S89 locus to 6p23.05-24.2. Cytogenet Cell Genet 60:37–39

Warner TT, Williams L, Harding AE (1994) DRPLA in Europe. Nature Genet 6:225

Weissenbach J, Gyapay G, Dib C, Vignal A, Morissette J, Millasseau P, Vaysseix G, et al (1992) A second generation linkage map of the human genome. Nature 359:794–801

Yakura H, Wakisaka A, Fujimoto S, Itakura K (1974) Hereditary ataxia and HLA genotypes. N Engl J Med 291:154–155

Zoghbi HY, Jodice C, Sandkuijl LA, Kwiatkowski TJ Jr, McCall AE, Huntoon SA, Lulli, P, et al (1991) The gene for autosomal dominant spinocerebellar ataxia (SCA1) maps telomeric to the HLA complex and is closely linked to the D6S89 locus in three large kindreds. Am J Hum Genet 49:23–30