periodic cerebellar ataxia: a problem of cerebellar intracellular pH homeostasis. Ann Neurol 31:147–154
Baloh RW, Winder A (1991) Acetazolamide-responsive vestibulocerebellar syndrome: clinical and oculographic features. Neurology 41:429–433
Bell GI, Karam JH, Rutter WJ (1981) Polymorphic DNA region adjacent to the 5′ end of the human insulin gene. Proc Natl Acad Sci USA 78:5759–5763
Browne D, Gancher ST, Nutt JG, Brunt ERP, Smith EA, Kramer P, Litt M (1994) Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene KCNA1. Nat Genet 8:1360140
Buetow KH, Weber JL, Ludwigsen S, Scherpbier-Heddema T, Duyk GM, Sheffield VC, Wang Z, et al (1994) Integrated human genome-wide maps constructed using the CEPH reference panel. Nat Genet 6:391–393
Gancher ST, Nutt JG (1986) Autosomal dominant episodic ataxia: a heterogeneous syndrome. Mov Disord 1:239–253
Gyapay G, Morisette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, et al (1994) The 1993–94 Génethon human genetic linkage map. Nat Genet 7:246–339
Joutel A, Bousser M-G, Biousse V, Labauge P, Chabriat H, Nibbio A, Maciazek J, et al (1993) A gene for familial hemiplegic migraine maps to chromosome 19. Nat Genet 5:40–45
Kramer P, Litt M, Browne D, Promchotikul T, Brunt ERP, Dubay C, Gancher S, et al (1994*a*) Autosomal dominant episodic ataxia represents at least two genetic disorders. Ann Neurol 36:279
Kramer P, Smith E, Carrero-Valenzuela R, Root D, Browne D, Lovrien E, Gancher S, et al (1994*b*) A gene for nystagmus-associated episodic ataxia maps to chromosome 19p. Am J Hum Genet Suppl 55:A191
Litt M, Hauge XY, Sharma V (1993) Shadow bands seen when typing polymorphic dinucleotide repeats: some causes and cures. Biotechniques 15:280–284
Litt M, Kramer P, Browne D, Gancher S, Brunt ERP, Root D, Phromchotikul T, et al (1994) A gene for episodic ataxia/myokymia maps to chromosome 12p13. Am J Hum Genet 55:702–709
Ptacek L (1994) Ion channel shake-down. Nat Genet 8:111–112
Schaffer AA, Gupta SK, Shiram K, Cottingham RW (1994) Avoiding recomputation in genetic linkage analysis. Hum Hered 44:225–237
Vahedi K, Joutel A, Van Bogaert P, Ducros A, Maciazeck J, Bach JF, Bousser MG, et al (1995) A gene for hereditary paroxysmal cerebellar ataxia maps to chromosome 19p. Ann Neurol 37:289–293
von Brederlow B, Hahn AF, Koopman WJ, Ebers GC, Bulman D (1995) Mapping the gene for acetazolamide responsive hereditary paroxysmal cerebellar ataxia to chromosome 19p. Hum Mol Genet 4:279–284
Zasorin NL, Baloh RW, Myers LB (1983) Acetazolamide-responsive episodic ataxia syndrome. Neurology 33:1212–1214

© 1995 by The American Society of Human Genetics. All rights reserved.
0002-9297/95/5701-0021$2.00

Am. J. Hum. Genet. 57:185–189, 1995

The Spinocerebellar Ataxia 2 Locus Is Located within a 3-cM Interval on Chromosome 12q23-24.1

To the Editor:

The autosomal dominant cerebellar ataxias (ADCA) are a clinically heterogeneous group of neurodegenerative disorders characterized by a predominantly cerebellar syndrome of onset with gait ataxia, dysarthria, dysmetria, and dysdiadochokinesia. Pathologically, the disorders are characterized by premature neuronal loss in the cerebellar cortex and the inferior olivary and pontine nuclei, with degeneration of the spinal cord.

Genetic heterogeneity has been established, with disease loci assigned to chromosomes 6q (Jackson et al. 1977), 11 (Ranum et al. 1994), 12q (Twells et al. 1993), 14q (Takiyama et al. 1993; Stevanin et al. 1994) and 16q (Gardner et al. 1994). Two of these genes have been isolated, and the mutation mechanism has been shown to be unstable $(CAG)_n$ motifs present within coding sequence (Orr et al. 1993; Kawaguchi et al. 1994).

Elsewhere, we have assigned the spinocerebellar ataxia 2 locus to chromosome 12q23-24.1, within a 31-cM interval flanked by the loci D12S58 and PLA2 (Twells et al. 1993). Although initially ascertained in a potential founder population from the Holguin province, Cuba, mutation at this locus is not unique to the Cuban kindred. Linkage to SCA2 has been demonstrated in pedigrees from Europe, Japan (Sasaki et al. 1993), and North America (Lopes-Cendes et al. 1994), the latter study serving to refine the candidate region to a 16-cM interval.

We report here genetic analysis undertaken between SCA2 and nine microsatellite loci known to span 8 cM within this interval. A total of 176 individuals, including 121 affected members from 16 pedigrees, were included in the analysis. A description of the phenotype has been reported elsewhere (Orozco-Diaz et al. 1990). The order and sex-averaged distance (in cM) between these markers is as follows: cen–D12S353–(0.00)–D12S330–(0.02)–D12S84–(0.00)–D12S105–(0.00)–AFM240we1–(0.03)–AFM128yf1–(0.00)–AFM312yb1–(0.01)–D12S354–(0.02)–D12S79–qter. Primer sequences were obtained from the Genome Database or by one of us (J.W.). Microsatellite analysis was performed following PCR amplification incorporating 100 ng genomic DNA, 50 pmol each of the forward and reverse primer, 200 μM dGTP, dCTP, dTTP, 25 μM dATP, 10 μCi ^{35}S-dATP and 0.25 U *Taq* polymerase (Dynazyme) in a standard 25 μl reaction. Amplification was carried out following an initial denaturation at 95°C for 7 min

Figure 1 *A*, Identification of the proximal boundary for the interval containing the disease locus by the detection of a recombination event in descendants of HC-5/III9 that positions SCA2 distal to AFM240we1. The haplotype segregating with the disease in the kindred is indicated (*box*). Haplotypes shown in parentheses are inferred from the pedigree. *B*, Identification of the distal boundary for the interval containing the disease locus by the detection of a recombination event in individual HC-19/VI24 that positions SCA2 proximal to AFM312yb1. The haplotype segregating with the disease in the kindred is indicated (*box*). Haplotypes shown in parentheses are inferred from the pedigree.

by using 30 cycles of 94°C for 1 min, 55°C for 1 min, and 72°C for 1 min and a final extension at 72°C for 10 min. Products were resolved on 6% polyacrylamide gels.

Pairwise lod scores between SCA2 and the polymorphic loci were calculated using MLINK from the LINKAGE 5.1 package (Lathrop et al. 1984), including affected members of the pedigrees only, to minimize dependence on presymptomatic individuals in the analysis. Several previously unreported alleles were observed in the course of analyzing these markers through the Cuban population, necessitating amendment of the frequencies according to observations made in individuals marrying into the kindred.

Lod scores for combined sexes ($\theta_{male} = \theta_{female}$) are reported in table 1. Evidence for tight linkage was observed for all markers, with no recombination detected between SCA2 and the loci D12S105 ($Z_{max} = 27.59$) and AFM128yf1 ($Z_{max} = 32.10$). Evidence for a common ancestral haplotype segregating with the disease in each of the 16 pedigrees was observed. The haplotype is defined by the alleles: D12S353 (allele 3 [103 bp])–D12S330 (allele 13 [166 bp])–D12S84 (allele 3 [219 bp])–D12S105 (allele 4 [147 bp])–AFM240we1 (allele

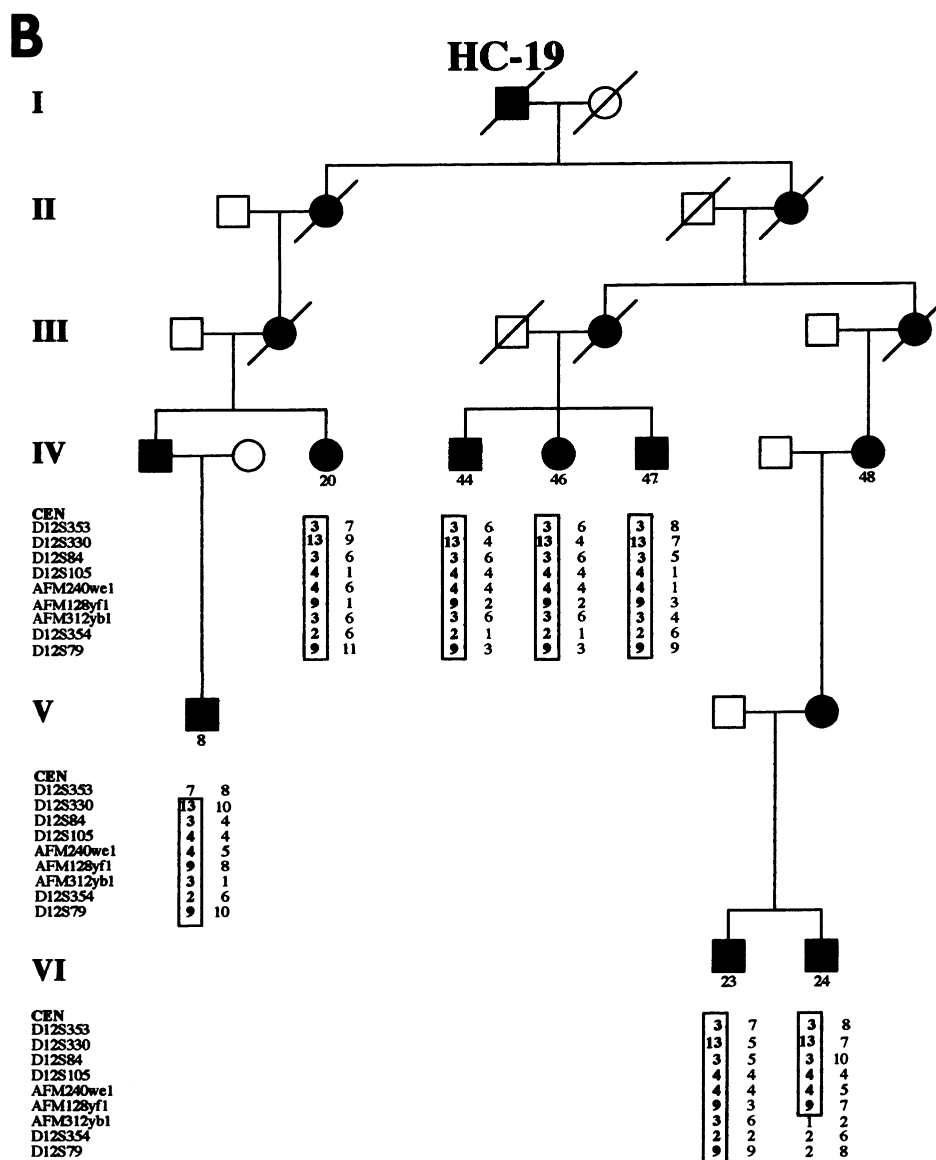

Figure 1 (continued)

4 [272 bp])–AFM128yf1 (allele 9 [208 bp])–AFM312yb1 (allele 3 [213 bp])–D12S354 (allele 2 [197 bp])–D12S79 (allle 9 [159 bp]). Concordance for segregation with a single allele at each locus is particularly strong within the interval defined by the loci D12S84–D12S354, providing independent evidence for the location of the SCA2 locus.

Critical recombination events that position the disease locus more precisely within this interval are shown in figure 1*A* and *B;* both pedigrees have been amended for brevity. The identification of the proximal boundary for the candidate region is derived from the interpretation of the genetic analysis of pedigree HC-5 (fig. 1*A*). Linkage to the SCA2 locus was independently confirmed in this pedigree by the generation of a maximal lod score of 3.76 (θ_{max} = .00) with the locus D12S105. Comparison of the disease haplotype in descendants of individual III9 with the ancestral haplotype observed in descendants of II2, III12, and III13 indicates the occurrence of a recombination event proximal to the locus AFM128yf1, as detected in the sibship IV1–IV5. The segregation of the disease haplotype in all affected members of the pedigree with markers telomeric to AFM240we1 confirms a distal location for SCA2 with respect to this locus.

The distal boundary to the SCA2 region is established by the detection of recombination events between the disease locus and the marker AFM312yb1 in affected

Table 1

Pairwise Lod Scores Generated between the SCA2 Locus and Microsatellite Loci Mapping to 12q23-24.1 by Using "Affected-Only" Analysis

Loci	Lod Score at Recombination Fractions (θ)							Z_{max}	θ_{max}
	.00	.01	.05	.10	.20	.30	.40		
D12S353	−1.86	13.55	14.84	13.78	10.05	5.84	2.19	14.87	.04
D12S330	−9.26	3.03	5.77	5.98	4.67	2.79	1.03	6.03	.08
D12S84	17.10	23.67	22.73	20.33	14.70	8.76	3.39	23.72	.02
D12S105	27.59	26.98	24.71	21.77	15.67	9.48	3.88	27.59	.00
AFM240we1	21.67	22.79	21.87	19.53	14.04	8.39	3.44	22.81	.02
AFM128yf1	32.10	31.48	28.95	25.69	18.80	11.59	4.80	32.10	.00
AFM312yb1	7.67	11.31	10.62	9.26	6.38	3.62	1.39	11.31	.01
D12S354	−4.87	4.33	5.26	4.76	3.14	1.66	.60	5.26	.04
D12S79	−24.04	2.74	7.35	7.92	6.37	3.95	1.69	7.94	.09

NOTE.—The markers define a linkage group spanning an 8-cM interval: cen–D12S353–(0.00)–D12S330–(0.02)–D12S84–(0.00)–D12S105–(0.00)–AFM240we1–(0.03)–AFM128yf1–(0.00)–AFM312yb1–(0.01)–D12S354–(0.02)–D12S79–qter.

members of two pedigrees. Haplotype analysis illustrating a distal recombination event in pedigree HC-19 in shown in figure 1*B*. Independent evidence for linkage of this pedigree to the chromosome 12 locus could be established with the locus D12S105 (Z_{max} = 8.43; θ_{max} = .00). Segregation of the full disease haplotype extending from D12S353–D12S79 is observed in affected family members. Evidence for recombination can be detected in the descendant (VI24) of individual IV48, where recombination away from the disease haplotype is detected distal to AFM128yf1, thus positioning SCA2 centromeric to AFM312yb1. Full phase could be constructed for the majority of markers proximal to this locus in this individual.

Interpretation of the recombination data strongly supports the location of the SCA2 gene within a 3-cM interval flanked by the markers AFM240we1 and AFM312yb1. The position of the D12S105 locus with respect to D12S84 and AFM340we1 could not be established for the construction of the Généthon genetic linkage map of the interval. The lack of recombination seen between SCA2 and D12S105 in this study would suggest a location for this marker distal to AFM340we1 and, hence, within the candidate interval. However, phase for this marker could not be assigned unequivocally in the key recombinant. Determination of the relative location of this marker awaits physical confirmation.

The identification of markers tightly linked to the SCA2 locus and in particular, D12S105 and AFM128yf1, will facilitate reliable genetic counseling. In the case of the Cuban kindred, the detection of a common ancestral haplotype segregating with the disease provides compelling evidence for the founder status of this population and, hence, strengthens the interpretation of data in those pedigrees of insufficient size and structure to allow linkage to be established independently.

Rebecca Allotey,[1] Rebecca Twells,[1]
Cemal Cemal,[1] Bruno Schleich Norte,[1]
Jean Weissenbach,[2] Mark Pook,[1]
Robert Williamson,[1] and Susan Chamberlain[1]
[1]*Department of Biochemistry and Molecular Genetics, St. Mary's Hospital Medical School, Imperial College, London; and* [2]*Généthon, Centre de Recherche sur le Genome Humain, Evry*

Acknowledgments

This project is supported by Action Research, the ATAXIA Group, U.K., and the Medical Research Council. We would like to thank Dr. Guillermo Orozco-Diaz and Professor Luis Heredero for their help in the collection and characterization of the pedigrees.

References

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 localization to chromosome 16 (SCA4) in a Utah kindred. Neurology 44:A361

Jackson JF, Currier RD, Terasaki PI and Morton NE (1977) Spinocerebellar ataxia and HLA linkage-risk prediction by HLA typing. N Engl J Med 296:1138–1141

Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, Kawakami H (1994) CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat Genet 8:221–227

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Lopes-Cendes I, Andermann E, Attig E, Cendes F, Bosch S, Wagner M, Gerstenbrand F, et al (1994) Confirmation of the *SCA-2* locus as an alternative locus for dominantly inherited spinocerebellar ataxias and refinement of the candidate region. Am J Hum Genet 54:774–781

Orozco-Diaz G, Fleites AN, Sagaz RC, Auburger G (1990) Autosomal dominant cerebellar ataxia: clinical analysis of 263 patients from a homogeneous population in Holguin, Cuba. Neurology 40:1369–1375

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

Ranum LPW, Schut LJ, Lundgren JK, Orr HT, Livingston DM (1994) Spinocerebellar ataxia type 5 in a family descended from the grandparents of President Lincoln maps to chromosome 11. Nat Genet 8:280–284

Sasaki H (1993) Linkage study of spinocerebellar ataxia and probable correlation for the loci to the disease phenotype. Rinsho Shinkeigaku 33:1285–1287

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 1 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. Nat Genet 4:300–304

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

© 1995 by The American Society of Human Genetics. All rights reserved.
0002-9297/95/5701-0022$2.00

Am. J. Hum. Genet. 57:189, 1995

BRCA1 Mutations in Ashkenazi Jewish Women

To the Editor:

The gene for breast and ovarian cancer, *BRCA1,* has recently been cloned (Miki et al. 1994). To date, we have identified *BRCA1* mutations in 24 North American families. In a recent collaborative report, the most common *BRCA1* mutation found was a 2-bp deletion in exon 2 (Shattuck-Eidens et al. 1995). This mutation (185delAG) was present in 6 of our 24 breast-ovarian cancer families. All six families are of Ashkenazi Jewish origin. The families are not known to be related to each other, but haplotype analyses suggest that these six families have a common ancestor (Simard et al. 1994). Only 1 of the other 18 families with *BRCA1* mutations was known to be of Jewish origin or had founders with surnames suggestive of Ashkenazi heritage ($P < .0001$). In total, six of the seven Ashkenazi families were found to carry the 185delAG mutation. Three other Ashkenazi families with this mutation have been reported by Struewing et al. (1995; in this issue). If the majority of hereditary breast-ovary cancer families in any ethnic subgroup can be attributed to a small number of mutations, our efforts to provide DNA-based predictive testing will be greatly enhanced.

PATRICIA TONIN,[1] OLGA SEROVA,[2] GILBERT LENOIR,[2] HENRY LYNCH,[3] FRANCINE DUROCHER,[4] JACQUES SIMARD,[4] KENNETH MORGAN,[1] AND STEVEN NAROD[1]

[1]*Division of Medical Genetics, Department of Medicine, and Department of Human Genetics, McGill University, Montreal;* [2]*International Agency for Research on Cancer, Lyon;* [3]*Creighton University School of Medicine, Department of Preventative Medicine and Public Health, Omaha; and* [4]*Laboratory of Molecular Endocrinology, CHUL Research Centre and Laval University, Quebec*

Acknowledgments

This work was supported by grants from the Canadian Genetic Diseases Network (Federal NCE program), the National Cancer Institute of Canada, the National Breast Cancer Research Initiative, Endorecherche, and the Department of the Army (United States) grant DAMD17-94-J-4299. S.N. is a fellow of the Fonds de la Recherche en Sante du Qûebec. J.S. is a scholar the Medical Research Council of Canada (MRC). F.D. is a recipient of a studentship from the MRC.

References

Miki Y, Swenson J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavitgan S, Lui Q, et al (1994) A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1.* Science 266:66–71

Shattuck-Eidens D, McClure M, Simard J, Labrie F, Narod S, Couch F, Hoskins K, et al (1995) A collaborative survey of 80 mutations in the *BRCA1* breast and ovarian cancer susceptibility gene. JAMA 273:535–541

Simard J, Tonin P, Durocher F, Morgan K, Rommens J, Gingras S, Samson C, et al (1994) Common origins of *BRCA1* mutations in Canadian breast and ovarian cancer families. Nat Genet 8:392–398

Struewing JP, Brody LC, Erdos MR, Kase RG, Giambarresi TR, Smith SA, Collins FS, et al (1995) Detection of eight *BRCA1* mutations in 10 breast/ovarian cancer families, including 1 family with male breast cancer. Am J Hum Genet 57:1–7 (in this issue)

© 1995 by The American Society of Human Genetics. All rights reserved.
0002-9297/95/5701-0023$2.00