Am. J. Hum. Genet. 68:523–528, 2001

Report

Ancestral Origins of the Machado-Joseph Disease Mutation: A Worldwide Haplotype Study

C. Gaspar,[1,2] I. Lopes-Cendes,[1] S. Hayes,[1] J. Goto,[4] K. Arvidsson,[1] A. Dias,[1,2] I. Silveira,[1,2] P. Maciel,[1,2] P. Coutinho,[3] M. Lima,[5] Y.-X. Zhou,[6] B.-W. Soong,[7] M. Watanabe,[8] P. Giunti,[9] G. Stevanin,[10] O. Riess,[11] H. Sasaki,[12] M. Hsieh,[13] G. A. Nicholson,[14] E. Brunt,[15] J. J. Higgins,[16] M. Lauritzen,[17] L. Tranebjaerg,[18] V. Volpini,[19] N. Wood,[9] L. Ranum,[20] S. Tsuji,[4] A. Brice,[10] J. Sequeiros,[2] and G. A. Rouleau[1]

[1]Centre for Research in Neuroscience, McGill University and The Montreal General Hospital Research Institute, Montreal; [2]UnIGENe, Instituto de Biologia Molecular e Celular, Universidade do Porto, and [3]Hospital Santo António, Porto, Portugal; [4]Department of Neurology, Institute for Brain Research, Niigata University, Niigata, Japan; [5]Department of Biology, Universidade dos Açores, Ponta Delgada, Açores, Portugal; [6]Department of Neurology, Neurogenetics Unit, China-Japan Friendship Hospital, Beijing; [7]Neurological Institute, Veterans General Hospital, Taipei, Taiwan, Republic of China; [8]Department of Neurology, Gunma University School of Medicine, Gunma, Japan; [9]Neurogenetics, Institute of Neurology, University of London, London; [10]Laboratoire de Médecine Experimentale, INSERM U 289, Hôpital de la Salpétrière, Paris; [11]Department of Molecular Human Genetics, Ruhr-University, Bochum, Germany; [12]Department of Neurology, Hokkaido University School of Medecine, Sapporo, Japan; [13]Chung Shan Medical and Dental College, Taichung, Taiwan, Republic of China; [14]Molecular Medecine Laboratory, University of Sydney Department of Medicine, Concord Hospital, Sydney, Australia; [15]Academish Ziekenhuis Groningen, Groningen, The Netherlands; [16] Clinical Neurogenetics Unit, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda; [17]Department of Clinical Neurophysiology, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark; [18]Department of Medical Genetics, University Hospital of Trömso, Trömso, Norway, [19]Medical and Molecular Genetics Centre-IRO, Hospital Duran i Reynals, Barcelona; and [20]Department of Neurology and Institute of Human Genetics, University of Minnesota, Minneapolis

Machado-Joseph disease (MJD) is an autosomal dominant neurodegenerative disorder originally described in families of Portuguese-Azorean ancestry. The cloning of the *MJD1* gene allowed identification of the disease in many other populations, and MJD is now known to be the most common cause of dominant spinocerebellar ataxia. The hypothesis that its present world distribution could result from the spread of an original founder mutation has been raised, both at historical and molecular levels. In the present study, we tested this hypothesis by linkage-disequilibrium analysis of tightly linked polymorphisms and by haplotype comparison, in 249 families from different countries. We typed five microsatellite markers surrounding the *MJD1* locus (D14S1015, D14S995, D14S973, D14S1016, and D14S977), and three intragenic single–base-pair polymorphisms (A^{669}TG/G^{669}TG, C^{987}GG/G^{987}GG, and TAA^{1118}/TAC^{1118}). The results show two different haplotypes, specific to the island of origin, in families of Azorean extraction. In families from mainland Portugal, both Azorean haplotypes can be found. The majority of the non-Portuguese families also share the same intragenic haplotype seen in the families coming from the island of Flores, but at least three other haplotypes were seen. These findings suggest two introductions of the mutation into the Portuguese population. Worldwide, the sharing of one intragenic haplotype by the majority of the families studied implies a founder mutation in MJD.

Machado-Joseph disease (MJD [MIM 109150]) is an autosomal dominant spinocerebellar degeneration associated with a variety of clinical manifestations, including ataxia, progressive external ophthalmoplegia, pyramidal signs, dystonia with rigidity, and distal myotrophies (Coutinho et al. 1977; Coutinho and Andrade 1978). The first descriptions of MJD came from families originating from the islands of the Azores (Nakano et al. 1972; Woods and Schaumburg 1972; Rosenberg et al. 1976), but the disease was later identified in families from many other ethnic origins (Sequeiros and Coutinho

Received September 1, 2000; accepted for publication November 29, 2000; electronically published December 20, 2000.

Address for correspondence and reprints: Dr. Guy A. Rouleau, L7-224, Montreal General Hospital, 1650 Cedar Avenue, Montréal, Québec H3G 1A4, Canada. E-mail: mi32@musica.mcgill.ca

0002-9297/2001/6802-0025$02.00

Table 1

Overall LD Analysis

Marker	Allele	δ	P
D14S1015	2	.11	.02
	6	.38	.001
A/G	A	.66	.001
C/G	C	.74	.001
C/A	A	.77	.001
D14S973	3	.39	.001
D14S1016	7	.44	.001
	10	.18	.001
D14S977	3	.16	.001
	6	.15	.001
D14S995	11	.37	.001

1993) and is now known to be the most common of the dominant spinocerebellar ataxias (Ranum et al. 1995; Schöls et al. 1995; Silveira et al. 1998).

The ancestral origin of the MJD mutation and the presence of a founder effect that would account for the worldwide distribution of the disease have been the source of much speculation over the years (Sequeiros 1989; Sequeiros and Coutinho 1993; Stevanin et al. 1995; Takiyama et al. 1995; Gaspar et al. 1996; Stevanin et al. 1997). In the Azores, the disease is mainly present in two islands, São Miguel and Flores. A founder effect was thought to account for the high frequency of MJD in the archipelago; the mutation would have arisen in mainland Portugal and later would have been introduced into the isolated Azorean archipelago during its colonization (Sequeiros and Coutinho 1993). The Portuguese sea travels of the late-15th and 16th centuries could explain the presence of MJD in countries like India, China, Japan, and others.

The MJD *locus* was mapped to chromosome 14q32.1 (Takiyama et al. 1993), the gene was identified (Kawaguchi et al. 1994), and the causative mutation was shown to be the expansion of a polymorphic CAG repeat within the coding region of a novel gene, *MJD1*. Several researchers previously have conducted linkage disequilibrium (LD) analyses between the *MJD1* locus and marker alleles surrounding it (Stevanin et al. 1995; Takiyama et al. 1995; Gaspar et al. 1996; Stevanin et al. 1997). We and others found preliminary evidence consistent with the existence of a founder mutation in MJD; surprisingly, our results were also suggestive of two distinct haplotypes in each of the islands of São Miguel and Flores (Gaspar et al. 1996); however, several factors rendered our results inconclusive, and recombination events giving rise to the different haplotypes could not be ruled out completely.

In an attempt to gain insight into the ancestral origin and spread of the MJD mutation, we performed an extensive haplotype study using five closely linked markers and three intragenic single–base-pair polymorphisms, in a large group of families representing the world population affected with MJD. Here we present evidence that supports the existence of one intragenic haplotype associated with the *MJD1* allele in the majority of the world MJD families, and we confirm the existence of two different haplotypes in the Azores and mainland Portugal.

Included in this study were 249 families affected by MJD, with various ethnic backgrounds. The origins of the families were: the Azores (specifically the islands of Flores, São Miguel, and Graciosa), mainland Portugal, Brazil, Spain, China, Taiwan, Germany, Japan, France, the United Kingdom, Belgium, Canada, the United States, Norway, India, the British West Indies, Ghana, Holland, Yemen, Morocco, French Guyana, Cambodia, the Ivory Coast, and Algeria. To determine genotype phase, we selected one affected individual from each family and both parents, when available, for a total of 601 individuals. Control subjects consisted of 388 unrelated individuals matched for ethnic origins to our study's MJD population; of these, 124 individuals (with no known links to any of the MJD families) were specifically collected in the islands of Flores and São Miguel in the Azores and were used as controls for the Azorean MJD subpopulation.

Blood samples were obtained from individuals after informed consent was obtained. Genomic DNA was extracted from lymphocytes or from MJD pathological material, following standard procedures (Sambrook et al. 1989).

Five microsatellite markers flanking the *MJD1* locus—D14S1015, D14S995, D14S973, D14S1016, and D14S977—and three intragenic single–base-pair polymorphisms were genotyped in the families and control individuals. The three intragenic markers were $\underline{A}^{669}$TG/$\underline{G}^{669}$TG, $\underline{C}^{987}$GG/$\underline{G}^{987}$GG, and a polymorphism involving the STOP codon, TA$\underline{A}^{1118}$/TA$\underline{C}^{1118}$ (Goto et al. 1997; Maciel et al. 1999). For simplification, these polymorphisms will be referred to as "A/G," "C/G," and "A/C," respectively.

Amplification of the A/G polymorphism was carried out using primers MJD1VSR (TACTAGAGCTTATTTGCCAG) and MJD734R (CAGAGCCCTCTGCAAATCCT). PCR products were visualized by SSCP analysis using a 0.5% MDE gel (FMC BioProducts) containing 5% glycerol. Amplification conditions were as follows: initial denaturation for 5 min at 94°C, followed by 30 cycles of 1 min at 94°C, 1 min at 56°C, and 1 min at 72°C, and a final elongation step of 5 min at 72°C.

Detection of the C/G polymorphism was achieved by allele-specific PCR using primers ASP1 (ACTCTGTCCTGATAGGTCCCC) or ASP2 (ACTCTGTCCTGATAGGTCCCG), in combination with MJD52 (Kawaguchi et al. 1994). The STOP codon polymorphism A/C was also detected by allele-specific PCR using primers

ASP3 (GCAAAAATCACATGGAGCTCT) or ASP4 (GCAAAAATCACATGGAGCTCG), together with MJD52. In both cases, PCR was performed using conditions described elsewhere (Kawaguchi et al. 1994), except for the annealing step, which was performed at 61°C for 30 s.

Only phase-known genotypes were included in the statistical analysis of LD between marker alleles and the *MJD1* allele. Differences in the overall distribution of alleles on normal and disease chromosomes were tested by Fisher's exact test. Evidence for LD was established using $\delta = (F_d - F_c)/(1 - F_c)$, where F_d is the frequency of carrier and F_c is the frequency of noncarrier chromosomes. A measure of allele-specific association, δ is an approximation of the population-attributable risk and has desirable properties in a case/control study (Devlin and Risch 1995). Nonsegregating alleles/haplotypes were used for determination of allele/haplotype frequency.

LD analysis in the overall MJD population revealed significant results for at least one (and sometimes more than one) allele for each marker (table 1). This result could be indicative of haplotypes common to major clusters of families that stand out in the overall group. At the intragenic level, values of δ were high for alleles forming the A-C-A haplotype, suggesting that this haplotype is common to most of the families under study. The results presented in table 1 seem to indicate that the A-C-A intragenic haplotype is conserved among most families affected with MJD and is associated with several different surrounding haplotypes. Detailed analysis of the overall intragenic haplotype frequencies in families affected by MJD and in control subjects (fig. 1 and table 2) revealed that all eight possible haplotypes defined by the three intragenic polymorphisms occur in the control population. In the families affected with MJD, only four of these haplotypes were detected (A-C-A, G-G-C, A-G-A, and G-C-C); however, in the majority (72%) of families, the disease allele was associated with the haplotype formed by marker alleles A, C, and A. Interestingly, A-C-A is the least common of the combinations found in the control population, with a frequency of only 2%. The G-G-C haplotype was significantly associated with the disease allele in the families affected with MJD, even

Table 2

Overall Linkage Disequilibrium Analysis for Intragenic Haplotypes

Haplotype	Frequency in Control Subjects	Frequency in Subjects with MJD	δ	P[a]
A-C-A	.02	.72	.71	<.001
A-C-C	.06	0	...	...
A-G-A	.04	.03	.01	NS
A-G-C	.13	0	...	...
G-C-A	.06	0	...	...
G-C-C	.19	0	...	...
G-G-A	.12	.01	.12	NS
G-G-C	.38	.22	.26	.003

[a] NS = not significant.

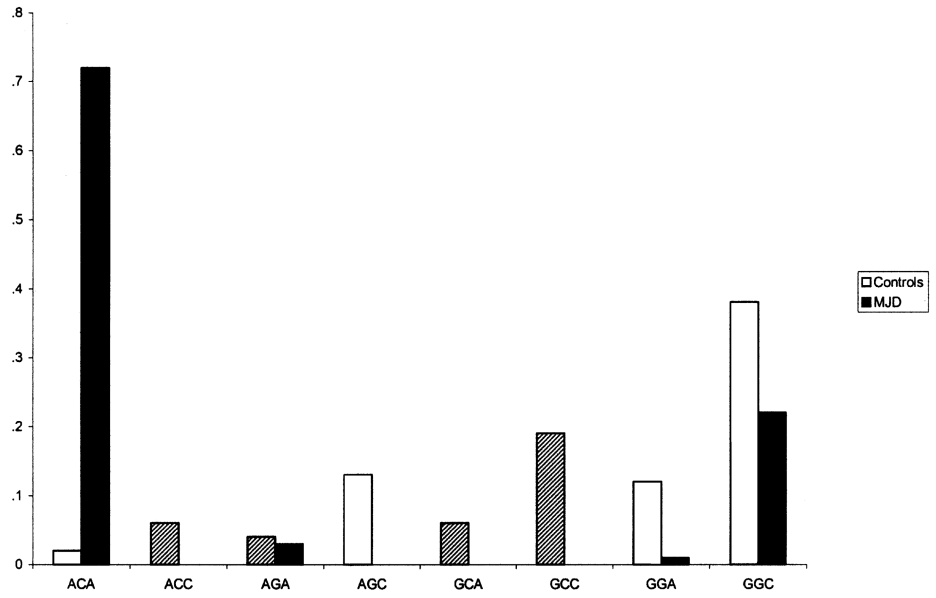

Figure 1 Overall intragenic haplotype frequencies. Frequency of the eight possible haplotypes formed by the three intragenic polymorphisms. All eight combinations were present in the control population; in contrast, only four of the possible haplotypes were seen in the MJD families, with haplotype A-C-A being present in >70% of the total MJD families used in this study.

Table 3

Intragenic Haplotypes in the Portuguese/Azorean Families

Haplotype	Flores (n = 10)	São Miguel (n = 12)	Graciosa (n = 1)	Mainland Portugal (n = 7)
A-C-A	9	0	0	4
G-G-C	1	12	1[a]	3

NOTE.—"n" represents number of families for which full phase-known haplotypes were determined at the three markers.

[a] Same extended haplotype seen in São Miguel.

though it is also the most common haplotype in the control population.

To investigate the sources of specific haplotypes, we proceeded to divide our collection of families affected by MJD into groups with similar ethnic origins. We started by constructing haplotypes for the Portuguese and North American families originating from the Azores (table 3). We analyzed a total of 23 families originating from the island of Flores, 15 families from the island of São Miguel, and 1 family from the island of Graciosa (table 3 depicts only the full phase-known haplotypes at the three markers; partial haplotypes are not represented but are consistent with the full haplotypes). The intragenic haplotype (A-C-A) associated with MJD in families from Flores differed, at all three polymorphic sites, from the haplotype observed in families from São Miguel (G-G-C). The D14S1015-D14S973-D14S1016-D14S977-D14S995 haplotypes in the two islands were also different, with 6-3-7-6-11 being the major haplotype in Flores, and 2-3-10-3/1-11 being the most common haplotype in São Miguel; other variants of the principal haplotype were found in families from both islands, probably due to recombination events. Also, one family from Flores presented with the G-G-C intragenic haplotype and other alleles characteristic of the São Miguel families. The family from Graciosa had the full 2–G-G-C–3–10–1–11 haplotype, the same as São Miguel. For Portuguese families originating from the mainland, both intragenic haplotypes were detected.

Haplotype analysis in the families of non-Portuguese origin was performed next (table 4). Kindreds from countries with links to Portugal, such as Brazil and Spain, were analyzed first: as was observed in mainland Portugal, both A-C-A and G-G-C intragenic haplotypes were detected. Inspection of the families with no obvious links to Portugal revealed the presence of the A-C-A intragenic haplotype in the vast majority of the families. Exceptions included (1) the G-G-C haplotype in five kindreds (Japan, British West Indies, and three families from the United States), (2) an A-G-A haplotype in three families (Morocco and two families from the United States), and (3) a G-G-A haplotype in one family from French Guyana.

Interestingly, haplotypes for the surrounding markers also provide some clues on the origin of the MJD mutation. Even though families from most countries in the world shared the same intragenic A-C-A haplotype, we observed the presence of various flanking haplotypes associated with it. Furthermore, some of the extended flanking haplotypes seemed to be specific to the country of origin of the family, although there was variability for these haplotypes, even between families from the same country (there was not enough uniformity to perform a statistical analysis). Interestingly, some of the French families share the extended haplotype seen for the families from the island of Flores.

The finding that families originating from 16 different countries from four continents share the same very rare intragenic haplotype strongly suggests that this haplotype has a common ancestry. We propose that the mutational event associated with the A-C-A haplotype accounts for the presence of MJD in most countries in the world. The fact that, in individual populations, this A-C-A haplotype is associated with particular haplotypes formed by some of the five markers surrounding the *MJD1* gene seems to indicate that (1) a single MJD mutation was introduced in various populations, followed by a local founder effect; and (2) this mutational event is probably very old, since the extended haplotypes are specific to the country of origin of the family. The G-G-C haplotype found in São Miguel and in a small number of other families probably resulted from a different mutational event. Other rare haplotypes found in countries like Morocco, the United States, and French Guyana are probably the result of independent mutations. Of these rare haplotypes, A-G-A and G-G-A, we could speculate that the latter resulted from the G-G-C haplotype by

Table 4

Intragenic Haplotypes in the Non-Portuguese Families

Country of Origin	Intragenic Haplotype			
	A-C-A	G-G-C	A-G-A	G-G-A
Japan (n = 16)	15	1	…	…
France (n = 12)	12	…	…	…
United States (n = 11)[a]	6	3	2	…
Germany (n = 9)	9	…	…	…
China/Taiwan (n = 6)	6	…	…	…
Brazil (n = 5)	4	1	…	…
Spain (n = 4)	2	2	…	…
Holland (n = 1)	1	…	…	…
Norway (n = 1)	1	…	…	…
Cambodia (n = 1)	1	…	…	…
Ivory Coast (n = 1)	1	…	…	…
British West Indies (n = 1)	1	…	…	…
Yemen (n = 2)	2	…	…	…
Morocco (n = 1)	…	…	1	…
French Guyana (n = 1)	…	…	…	1

NOTE.—"n" represents number of families for which full phase-known haplotypes were determined at the three markers.

[a] These families do not include the North American MJD families that emigrated from the Azores.

recombination and could well represent the same haplotype; the A-G-A haplotype can hardly be explained by the occurrence of recombination at the A-C-A haplotype, since the intragenic polymorphisms are so close together, but this haplotype is rare enough that it could have resulted from A-C-A by a single-nucleotide substitution.

There now seems to be little doubt that two distinct mutational events account for the presence of MJD in the Azorean archipelago and in families of Azorean extraction. The completely distinct haplotypes observed in families from the two islands make it virtually impossible that a single mutation was introduced into the Azores. Genealogical studies performed by Lima et al. (1998) strongly confirm, and complement, our findings.

It is tempting to speculate on how this mutation spread, reaching the high prevalence it shows today. A late-onset disease of dominant transmission, such as MJD, could easily attain a relatively high frequency in diverse populations. Sequeiros and Coutinho suggested that the original mutational event occurred in mainland Portugal, spreading to the Azores with its colonization during the course of the 15th or 16th centuries and from there to the United States and Canada, with the waves of emigration from the archipelago at the end of last century (Sequeiros and Coutinho 1993). Links with other countries, more distant in time and space, could be accounted for by the Portuguese sea explorations starting in the mid-15th century. We cannot rule out, however, the possibility that the mutational event associated with the A-C-A haplotype took place among any of the other ethnic groups studied and was later brought to the Azores and mainland Portugal. We could speculate that the Flores mutation was introduced from France, for instance, since some families originating from both places share the same extended haplotype.

Another possibility is the existence of a haplotype that predisposes for MJD. We addressed this issue elsewhere (Maciel et al. 1999), using the same three intragenic polymorphisms reported here, and showed a lack of association between any of the intragenic haplotypes (including A-C-A) and larger $(CAG)_n$ alleles in the normal population, suggesting the absence of a predisposing haplotype. It would be interesting to extend this study to a larger and ethnically diverse control population.

In summary, our findings suggest the existence of two introductions of the mutation into the Portuguese population. We show evidence worldwide for the existence of a founder mutation accounting for the present distribution of Machado-Joseph disease.

Acknowledgments

The authors would like to thank the families for their participation in our study, and Marylène Rousseau for assistance in genotyping the samples. This work was supported by the NIH (grant NS31687). C.G. is the recipient of a scholarship from Junta Nacional de Investigação Científica e Tecnológica (Praxis XXI), Portugal, and G.A.R. is supported by the Medical Research Council of Canada.

Electronic-Database Information

The accession number and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Machado-Joseph disease [MIM 109150])

References

Coutinho P, Andrade C (1978) Autosomal dominant system degeneration in Portuguese families of the Azores Islands: a new genetic disorder involving cerebellar, pyramidal, extrapyramidal and spinal cord motor functions. Neurology 28: 703–709

Coutinho P, Calheiros JM, Andrade C (1977) Sobre uma nova doenca degenerativa do sistema nervoso central transmitida de modo autossomico dominante e aspectos familiares originarios dos Acores. O Médico 82:1–3

Devlin B, Risch N (1995) A comparison of linkage disequilibrium measures for fine-scale mapping. Genomics 29: 311–322

Gaspar C, Lopes-Cendes I, DeStefano AL, Maciel P, Silveira I, Coutinho P, MacLeod P, Sequeiros J, Farrer LA, Rouleau GA (1996) Linkage disequilibrium analysis in Machado-Joseph disease patients of different ethnic origins. Hum Genet 98:620–624

Goto J, Watanabe M, Ichikawa Y, Yee SB, Ihara N, Endo K, Igarashi S, Takiyama Y, Gaspar C, Maciel P, Tsuji S, Rouleau GA, Kanazawa I (1997) Machado-Joseph disease gene products carrying different carboxyl termini. Neurosci Res 28: 373–377

Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S, Kawakami H, Nakamura S, Nishimura M, Akiguchi I, Kimura J, Narumiya S, Kakizuka A (1994) CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nature Genetics 8:221–228

Lima M, Mayer FM, Coutinho P, Abade A (1998) Origins of a mutation: population genetics of Machado-Joseph disease in the Azores (Portugal). Hum Biol 70:1011–1023

Maciel P, Gaspar C, Guimarães L, Goto J, Lopes-Cendes I, Hayes S, Arvidsson K, Dias A, Sequeiros J, Sousa A, Rouleau GA (1999) Study of three intragenic polymorphisms in the Machado-Joseph disease gene (*MJD1*) in relation to genetic instability of the (CAG)n tract. Eur J Hum Genet 7:147–156

Nakano KK, Dawson DM, Spence A (1972) Machado disease. A hereditary ataxia in Portuguese emigrants to Massachusetts. Neurology 22:49–55

Ranum LP, Lundgren JK, Schut LJ, Ahrens MJ, Perlman S, Aita J, Bird TD, Gomez C, Orr HT (1995) Spinocerebellar ataxia type 1 and Machado-Joseph disease: incidence of CAG expansions among adult-onset ataxia patients from 311 families with dominant, recessive, or sporadic ataxia. Am J Hum Genet 57:603–608

Rosenberg RN, Nyhan WL, Bay C, Shore P (1976) Autosomal

dominant striatonigral degeneration: a clinical, pathologic, and biochemical study of a new genetic disorder. Neurology 26:703–714

Sambrook J, Fritsch EF, Maniatis T (1989) Molecular cloning: a laboratory manual. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY

Schöls L, Amoiridis G, Langkafel M, Buttner T, Przuntek H, Riess O, Vieira-Saecker AM, Epplan JT (1995) Machado-Joseph disease mutations as the genetic basis of most spinocerebellar ataxias in Germany. J Neurol Neurosurg Psychiatry 59:449–50

Sequeiros J (1989) Rise, travels and vicissitudes of a mutant gene: genetic epidemiology of Machado-Joseph disease. Clin Res 37:870A

Sequeiros J, Coutinho P (1993) Epidemiology and clinical aspects of Machado-Joseph disease. Adv Neurol 61:139–153

Silveira I, Coutinho P, Maciel P, Gaspar C, Hayes S, Dias A, Guimarães J, Loureiro L, Sequeiros J, Rouleau GA (1998) Analysis of SCA1, DRPLA, MJD, SCA2, and SCA6 CAG repeats in 48 Portuguese ataxia families. Am J Med Genet 81:134–138

Stevanin G, Cancel G, Didierjean O, Durr A, Abbas N, Cassa E, Feingold J, Agid Y, Brice A (1995) Linkage disequilibrium at the Machado-Joseph disease/spinal cerebellar ataxia 3 locus: evidence for a common founder effect in French and Portuguese-Brazilian families as well as a second ancestral Portuguese-Azorean mutation. Am J Hum Genet 57: 1247–1250

Stevanin G, Lebre AS, Mathieux C, Cancel G, Abbas N, Didierjean O, Durr A, Trottier Y, Agid Y, Brice A (1997) Linkage disequilibrium between the spinocerebellar ataxia 3/Machado-Joseph disease mutation and two intragenic polymorphisms, one of which, X359Y, affects the stop codon. Am J Hum Genet 60:1548–1552

Takiyama Y, Igarashi S, Rogaeva EA, Endo K, Rogaev EI, Tanaka H, Sherrington R, et al (1995) Evidence for intergenerational instability in the CAG repeat in the MJD1 gene and for conserved haplotypes at flanking markers amongst Japanese and Caucasian subjects with Machado-Joseph disease. Hum Mol Genet 4:1137–1146

Takiyama Y, Nishizawa M, Tanaka H, Kawashima S, Sakamoto H, Karube Y, Shimazaki H, Soutome M, Endo K, Ohta S, Kagawa Y, Kanazawa I, Mizumo Y, Yoshida M, Yuasa T, Horikawa Y, Oyanagi K, Nagai H, Kondo T, Inuzuka T, Onodera O, Tsuji S (1993) The gene for Machado-Joseph disease maps to human chromosome 14q. Nat Genet 4: 300–304

Woods BT, Schaumburg HH (1972) Nigro-spino-dentatal degeneration with nuclear ophthalmoplegia: a unique and partially treatable clinico-pathological entity. J Neurol Sci 17: 149–66