

Machado Joseph disease maps to the same region of chromosome 14 as the spinocerebellar ataxia type 3 locus

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Abstract

Machado Joseph disease (MJD) is an autosomal dominantly inherited neurodegenerative disorder primarily affecting the motor system. It can be divided into three phenotypes based on the variable combination of a range of clinical symptoms including pyramidal and extrapyramidal features, cerebellar deficits, and distal muscle atrophy. MJD is thought to be caused by mutation of a single gene which has recently been mapped, using genetic linkage analysis, to a 29 cM region on chromosome 14q24.3-q32 in five Japanese families. A second disorder, spinocerebellar ataxia type 3 (SCA3), which has clinical symptoms similar to MJD, has also been linked to the same region of chromosome 14q in two French families. In order to narrow down the region of chromosome 14 which contains the MJD locus and to determine if this region overlaps with the predisposing locus for SCA3, we have performed genetic linkage analysis in seven MJD families, six of Portuguese/Azorean origin and one of Brazilian origin, using nine microsatellite markers mapped to 14q24.3-q32. Our results localise the MJD locus in these families to an 11 cM interval flanked by the markers D14S68 and AFM343vfl. In addition we show that this 11 cM interval maps within the 15 cM interval containing the SCA3 locus, suggesting that these diseases are allelic.

(J Med Genet 1995;32:25-31)

Machado Joseph disease (MJD) is an inherited neurodegenerative disorder which primarily affects the motor system.¹ It shows an autosomal dominant pattern of transmission and a mean age of onset of 37.4 years (SD 14.1). Pathologically, there is neuronal loss in the dentate nucleus of the cerebellum as well as progressive loss of neurones and gliosis in the substantia nigra and basis pontis. In addition, there is significant motor neurone loss in the anterior horn of the spinal cord and in motor cranial nerve nuclei.²⁻⁷ The spinal cord also shows demyelination and there is atrophy of the spinocerebellar tracts. These morphological changes give rise to a wide range of clinical symptoms including cerebellar ataxia, pro-

gressive external ophthalmoplegia, pyramidal signs, dystonia, rigidity, amyotrophy, and peripheral neuropathy.^{3,5,8,9}

Based on the variable combination of these clinical symptoms in different persons, MJD can be divided into three phenotypes: type I begins in the second or third decade with pyramidal and extrapyramidal features and has a rapid clinical course; type II occurs most frequently in the second to fourth decade with predominantly cerebellar deficits; and type III begins in the fifth to seventh decade with distal muscle atrophy being the prominent feature.⁹ The reasons for such variation in clinical presentation remain to be established but genetic heterogeneity seems unlikely since different subtypes are frequently seen within the same family.^{9,10} In addition, the phenotype is not fixed but can change over time.^{5,9} Thus, it appears that MJD is the result of a single gene mutation which results in variable expression of the disease.¹⁰

MJD was initially described in three American families of Portuguese/Azorean descent.^{2,8,12} The disease is most prevalent (1:4000) in the Portuguese islands of the Azores, as well as in Portuguese Americans from New England and California. It is now generally accepted, however, that the disease also exists in other ethnic groups, for example, Japanese,^{7,13-17} Aboriginal Australians,¹⁸ black Americans,^{19,20} and Italian,^{21,22} Spanish, Russian, and Chinese kindreds from the USA as well as Spanish and Chinese kindreds from mainland Spain and China.²³ It is possible that these populations have links with Portugal or, alternatively, MJD may have arisen in these groups as a result of different ancestral mutations of the MJD gene.

The gene for MJD has recently been mapped to a 29 cM interval on chromosome 14q24.3-q32 in five Japanese kindreds.¹⁴ Subsequently, a second disorder, spinocerebellar ataxia type 3 (SCA3), has been mapped to the same region of chromosome 14q in two French families.²⁴ In order to narrow down the region of chromosome 14 which contains the MJD locus and to determine if this region overlaps with the predisposing locus for SCA3, we have performed genetic linkage analysis in seven families segregating MJD, six Portuguese/Azorean families, and one Brazilian family, using nine microsatellite markers mapped to 14q24.3-q32. Our results show that the MJD locus is localised to an 11 cM interval flanked by the

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Received 24 June 1994
Revised version accepted for publication 15 August 1994

Table 1 Machado Joseph families used for linkage analysis

Pedigree identification	No of persons sampled	No of persons affected	No of persons at risk
MJD-1	19	11	5
MJD-2	18	10	5
MJD-3A	9	3	4
MJD-3B	22	12	6
MJD-4	11	3	5
MJD-11	13	5	6
MJD-B1	101	32	56
Total	193	76	87

markers D14S68 and AFM343vf1. In addition we show that this 11 cM interval lies within the 15 cM interval containing the SCA3 locus, indicating that these diseases may be allelic.

Materials and methods

Seven pedigrees of known Portuguese/Azorean descent which were segregating MJD were selected for linkage analysis: five from New England (identified as MJD-1, MJD-2, MJD-3A, MJD-3B, and MJD-4), one from California (identified as MJD-11), and one from Santa Catarina, Brazil (identified as MJD-B1). All seven pedigrees have been described previously.²⁵⁻²⁷ Blood was collected from 193 persons, 76 of whom are affected and 87 of whom are at risk (table 1). DNA was extracted as previously described²⁸ and, in addition, lymphoblastoid cell lines were established by Epstein Barr virus transformation.²⁸

Linkage analysis was carried out using a range of highly informative di- and tetra-nucleotide repeat polymorphic markers (fig 1). Polymerase chain reaction (PCR) amplification of the desired fragments was carried out as described previously.²⁹ PCR reactions were subjected to a hot start of 94°C for two

minutes followed by 30 cycles of denaturing for one second at 94°C and then one minute at 92°C, annealing for 45 seconds at temperatures ranging from 52°C to 57°C depending on the primer pairs, and elongation for one minute at 72°C followed by a final extension of five minutes at 72°C and then cooling of the product to 4°C. DNA fragments were resolved on 5% or 6% polyacrylamide denaturing sequence gels for varying lengths of time depending on the size of the DNA fragment. Gels were dried and exposed to x ray film for three days.

Linkage between the MJD locus and the chromosome 14 markers was analysed by the computer program LIPED³⁰ using an age at onset correction function³¹ which assumed a normal distribution with a mean of 37.4 (SD 14.1),⁹ autosomal dominant transmission of MJD, and mutant allele frequency of 0.0005. Allele frequencies for the markers were calculated from genotype analysis of a sample of 30 spouses of family members.

The genetic map of chromosome 14 used to position the MJD locus (fig 1) was based on the Génethon map³² and the map according to Takiyama *et al.*¹⁴ Two additional markers, D14S124 and D14S128, were inserted into the map by multilocus linkage analysis. CEPH reference pedigree data were obtained from the Utah and Collaborative Human Linkage Center data bases. Odds for marker order and distances were estimated using the CRIMAP program.³³ The marker order D14S74-D14S55-D14S128-D14S124-D14S48-D14S51 was equally likely as the order D14S74-D14S55-D14S128-D14S48-D14S124-D14S51. However, haplotype analysis in the MJD families favoured the former order. This marker order was 1000:1 times more likely than any other possible order.³³ D14S68 was positioned according to Stevanin *et al.*²⁴

Evaluation of the support for linkage of MJD within each interval on the genetic map (fig 1) was carried out by multilocus linkage analysis using the LINKMAP program (version 4.9) from the LINKAGE package.³⁴ In these analyses, age dependent penetrance of MJD was defined as a step function based on 15 age intervals corresponding as closely as possible to the function used in the LIPED analyses. D14S48 and D14S124 were treated as a haplotype since recombination has not been observed between them. Computer analyses were facilitated by reducing the observed alleles for each marker to four using the scheme of Braverman³⁵ which is an implementation of a method proposed by Ott.³⁶ Allele reductions were done by hand. A series of overlapping four loci (MJD plus three marker loci) were carried out in a manner previously described,³⁷ which allowed comparison of results over all intervals and efficient computation. Because an age correction function may not adequately account for non-penetrance in some persons, analyses were repeated after changing the disease penetrance in all at risk persons to zero (that is, a zero penetrance model). This latter model is similar to an "affecteds only" model in that normal offspring contribute no linkage information with regard to MJD; however, they

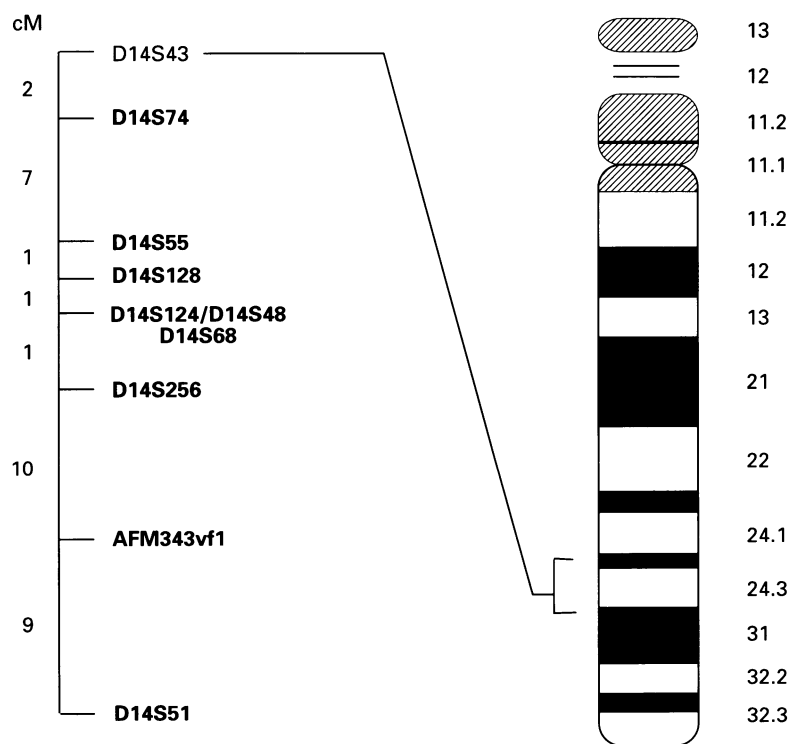


Figure 1 Linkage map of markers on chromosome 14q in the region of the MJD locus. Markers used in this study are highlighted in bold print.

Table 2 Pairwise lod scores between chromosome 14 markers and the Machado Joseph disease locus for individual families

	θ						Z_{max}	(θ)
	0.00	0.01	0.05	0.10	0.20	0.40		
<i>D14S48</i>								
MJD-B1	2.82	3.80	4.06	3.82	3.00	0.98		
MJD-1	-1.03	-0.53	0.01	0.24	0.39	0.23		
MJD-2	1.21	1.20	1.15	1.05	0.78	0.19		
MJD-3A	0.63	0.62	0.58	0.53	0.41	0.16		
MJD-3B	-∞	-1.12	-0.50	-0.26	-0.08	-0.01		
MJD-4	0.04	0.05	0.06	0.07	0.05	0.00		
MJD-11	0.87	0.86	0.81	0.72	0.51	0.07		
Total	-∞	3.88	6.17	6.17	5.06	1.62	6.25	0.07
<i>D14S51</i>								
MJD-B1	4.49	4.40	4.05	3.56	2.53	0.61		
MJD-1	-∞	-0.73	0.11	0.45	0.59	0.20		
MJD-2	-∞	-1.78	-0.83	-0.42	-0.11	0.00		
MJD-3B	-∞	-3.85	-1.94	-1.07	-0.32	0.03		
MJD-4	-0.05	0.00	0.12	0.17	0.17	0.00		
MJD-11	0.89	0.87	0.81	0.72	0.52	0.11		
Total	-∞	-1.09	2.32	3.41	3.38	0.95	3.41	0.10
<i>D14S55</i>								
MJD-B1	-∞	0.42	1.35	1.62	1.51	0.29		
MJD-1	-∞	-3.99	-2.38	-1.42	-0.58	-0.05		
MJD-2	-0.46	-0.43	-0.30	-0.19	-0.07	0.00		
MJD-3B	-∞	-2.48	-1.29	-0.73	0.23	0.05		
MJD-4	-0.73	-0.67	-0.49	-0.36	-0.21	-0.05		
MJD-11	-0.28	-0.27	-0.26	-0.22	-0.14	-0.02		
Total	-∞	-7.42	-3.37	-1.30	0.74	0.22	3.41	0.20
<i>D14S74</i>								
MJD-B1	-∞	1.10	2.05	2.12	1.68	0.39		
MJD-1	-∞	-0.59	0.02	0.20	0.26	0.10		
MJD-2	2.07	2.01	1.83	1.61	1.10	0.15		
MJD-3A	0.63	0.62	0.58	0.53	0.41	0.16		
MJD-3B	-1.11	-1.05	-0.33	0.13	0.36	0.07		
MJD-4	-∞	-1.29	-0.63	-0.37	-0.14	-0.01		
MJD-11	-∞	-3.17	-1.85	-1.17	-0.46	-0.03		
Total	-∞	-2.39	1.67	3.05	3.21	0.83	3.35	0.18
<i>D14S124</i>								
MJD-B1	-0.23	0.89	1.27	1.19	0.76	0.12		
MJD-1	-0.97	0.07	0.67	0.83	0.77	0.28		
MJD-2	1.69	1.65	1.53	1.36	1.00	0.23		
MJD-3B	0.73	0.71	0.64	0.55	0.36	0.04		
MJD-4	-0.19	-0.14	-0.02	0.06	0.11	0.04		
MJD-11	1.82	1.78	1.63	1.43	1.01	0.16		
Total	2.84	4.96	5.71	5.42	4.01	0.87	5.71	0.05
<i>D14S128</i>								
MJD-B1	-∞	1.79	3.28	3.46	2.84	0.68		
MJD-1	-0.70	0.44	1.03	1.17	1.03	0.31		
MJD-2	2.88	2.83	2.61	2.34	1.74	0.39		
MJD-3A	0.63	0.62	0.58	0.53	0.41	0.16		
MJD-3B	-∞	-1.12	-0.51	-0.28	-0.12	-0.03		
MJD-4	-∞	-0.82	-0.20	0.01	0.13	0.06		
MJD-11	2.32	2.27	2.07	1.82	1.29	0.21		
Total	-∞	6.01	8.86	9.05	7.32	1.78	9.13	0.08
<i>D14S256</i>								
MJD-B1	8.32	8.16	7.50	6.66	4.89	1.29		
MJD-1	2.06	2.04	1.95	1.80	1.38	0.38		
MJD-2	1.06	1.04	0.94	0.81	0.56	0.09		
MJD-3A	0.63	0.62	0.58	0.53	0.41	0.16		
MJD-3B	-∞	-1.79	-0.94	-0.52	-0.16	0.00		
MJD-4	0.64	0.61	0.53	0.43	0.25	0.04		
MJD-11	0.30	0.29	0.26	0.21	0.12	0.02		
Total	-∞	10.94	10.82	9.92	7.45	1.98	11.07	0.02
<i>AFM343vf1</i>								
MJD-B1	3.58	5.09	5.22	4.80	3.61	0.96		
MJD-1	1.70	1.68	1.59	1.43	1.05	0.20		
MJD-2	2.88	2.83	2.61	2.34	1.74	0.38		
MJD-3B	-∞	-1.67	-0.46	-0.01	0.25	0.10		
MJD-4	0.45	0.43	0.37	0.30	0.18	0.02		
MJD-11	0.99	1.04	1.12	1.10	0.87	0.17		
Total	-∞	9.40	10.45	9.96	7.70	1.83	10.45	0.05

provide valuable information about the marker genotype and linkage phase between markers in their parents, many of whom were unavailable for study.

Results

We have analysed nine di- and tetranucleotide repeat polymorphic markers spanning the 29 cM region of chromosome 14q24.3-q32.2, reported by Takiyama *et al*¹⁴ to contain the gene responsible for MJD (fig 1).

Two point lod scores between the MJD locus and each marker for all seven families examined are shown in table 2. The marker D14S68 is not included in the table since it was analysed in family MJD-B1 only, yielding a maximum lod score of 5.03 at a recombination fraction of 0.03. The cumulative lod scores for each marker was greater than +3 with the exception of D14S55 which was not very informative. D14S256 showed the highest lod score of 11.07 at a recombination fraction of 0.02. The maximum likelihood estimates of recombination

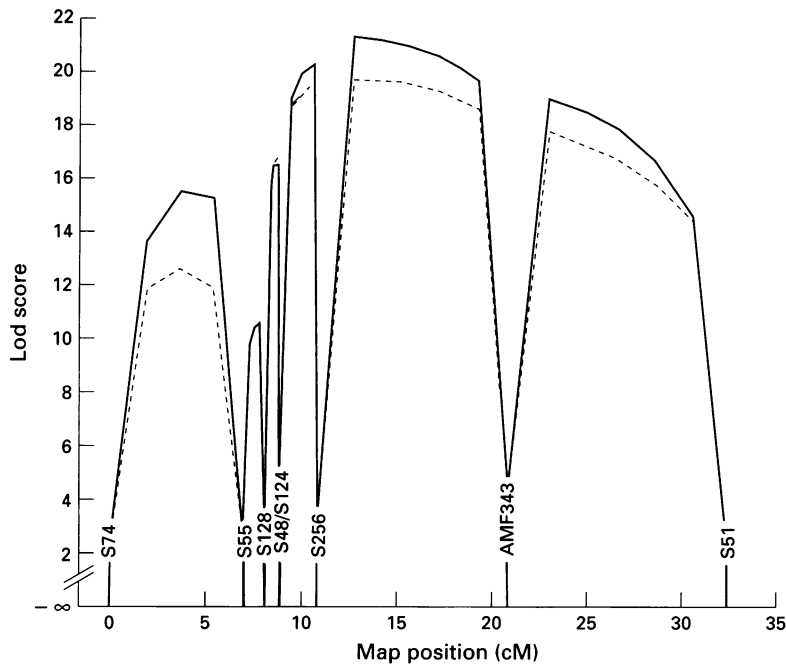


Figure 2 Support for position of the MJD locus with respect to chromosome 14 marker loci. The position of D14S74 was arbitrarily set at 0.00 and the positions of the other loci were fixed according to the genetic map in fig 1. The solid line indicates the support assuming age dependent penetrance and the dashed line indicates the support assuming incomplete penetrance in at risk persons.

for all other markers were greater than 0.02. Inspection of the lod scores by family shows that pedigree MJD-B1 is significantly linked (lod greater than 3.0) to D14S48, D14S128, D14S256, AFM343vf1, and D14S51. Lod scores greater than 2.0 were obtained in pedigrees MJD-1 (D14S256) and MJD-2 (D14S74, D14S128, D14S256, and AFM343vf1). The other pedigrees, which had fewer meiotic events, yielded positive lod scores greater than 0.5 with at least one marker. There was no evidence of linkage heterogeneity. Multilocus analysis was carried out using the genetic linkage map shown in fig 1, to determine the precise location of the MJD gene among the group of chromosome 14q markers analysed. The most likely location for the MJD gene is at a position 2 cM distal to D14S256 and 8 cM proximal to AFM343vf1. However, assuming a one lod unit confidence interval, the MJD gene is not excluded from any of the tested locations between these two flanking markers. The statistical support favouring each order is presented in fig 2. Odds against the second most likely order (the MJD gene being in the interval immediately proximal to D14S256) are 11 to 1. The other possible orders are much less likely ranging from 288 to 1 (the MJD gene being in the interval between AFM343vf1 and D14S51) to 5.75×10^{10} to 1 (the MJD gene being in the interval between D14S55 and D14S128). The final conclusion and relative position of the MJD gene between the flanking markers was unchanged if zero penetrance in at risk persons was assumed.

Haplotype analysis was carried out on all seven families. The most informative recombinants are shown in fig 3A and B which depict different branches of the largest pedigree, MJD-B1. Fig 3A shows recombination

of the chromosome inherited from the affected mother below the marker D14S256 in both subjects 24 and 86. In fig 3B, subject 538 (whose DNA has not been obtained) appears to have only inherited that portion of the chromosome from her affected parent below the marker D14S68. This can be inferred since her affected daughter, subject 98, only inherited this portion of the "affected" chromosome from her. In addition, her affected son, subject 540 (whose DNA has also not been obtained), has also inherited this portion of the "affected" chromosome as inferred from his affected daughter, subject 65. Thus, from these persons, the MJD gene can be localised to that interval below D14S68 and above AFM343vf1, a genetic distance of approximately 11 cM. There are, however, a number of persons who inherit this region of chromosome 14 from their affected parent but who are at present asymptomatic. These persons are below the mean age of onset, that is, below 37 years of age, with the exception of subject 26 who is 38 years.

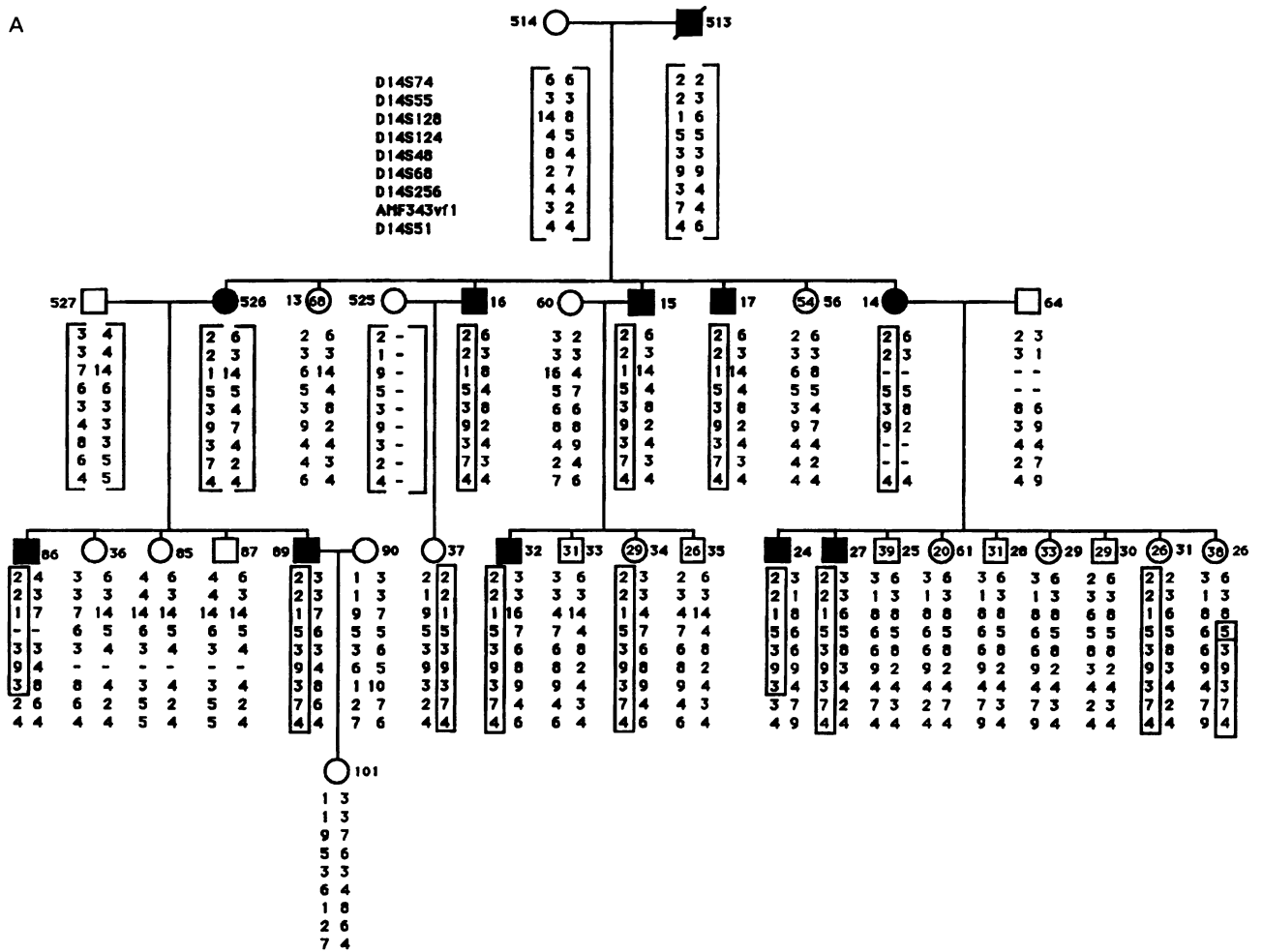
Discussion

In this paper we show that MJD segregating in seven Portuguese/Azorean families currently living in the United States and one Brazilian family is linked to chromosome 14q24.3-q32, confirming the findings of Takiyama *et al.*¹⁴ In their study, they found tight linkage of MJD to the markers D14S55 and D14S48 in five Japanese families. Multiple recombination events were observed between the more centromeric marker D14S53 and the MJD loci and between the more telomeric marker D14S45 and the MJD locus. Thus the gene for MJD was postulated to lie within a 29 cM region flanked by these two markers.

In our families a cumulative two point lod score of +6.25 and +0.74 was obtained with the markers D14S48 and D14S55 respectively with multiple recombination events being observed between both markers and the MJD locus. Our data suggest that the MJD gene is located 8 cM centromeric to AFM343vf1 and 2 cM telomeric to D14S256. From haplotype analysis it can be shown that the MJD locus maps within a 11 cM region flanked by the markers D14S68 and AFM343vf1. At least one recombination event is seen between D14S256 and the MJD locus in family MJD-3B, tentatively placing the MJD locus telomeric to this marker. However, since there are a number of generations of untyped persons in this pedigree, reconstruction of the recombinant haplotypes is problematical at present.

In this study, we did not find linkage disequilibrium with any of the marker loci tested. The evidence for linkage disequilibrium reported by Takiyama *et al.*¹⁴ is misleading since it appears that they included chromosomes from multiple members (affected and unaffected) from every MJD family. Their sample, which contains only five unrelated MJD chromosomes, is not sufficient for linkage disequilibrium studies. This fact notwithstanding, the multilocus one lod unit confidence interval for the most likely location of MJD in the

A



B

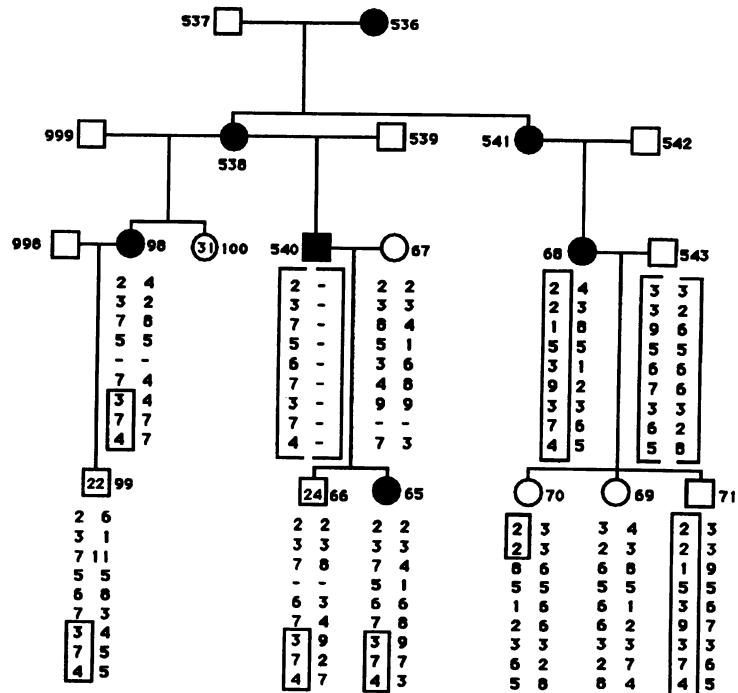


Figure 3A and B Haplotype analysis of part of the MJD-B1 kindred indicating a centromeric and a telomeric marker flanking the interval containing the MJD locus. The haplotype segregating with the disease is surrounded by a box. Bracketed haplotypes have been inferred from offspring. Age of at risk persons (where this information is available) is indicated within the symbol denoting sex.

Japanese families includes the most likely location for MJD in our group of families.

Recently, another type of autosomal dominant cerebellar ataxia, SCA3, has been linked to the same region of chromosome 14q as MJD.²⁴ The autosomal dominant cerebellar ataxias (ADCA) are clinically and genetically a heterogeneous group and, according to Harding,³⁸ can be divided into three types: ADCA type 1 can be further subdivided to include MJD, chromosome 6 linked SCA1, chromosome 12 linked SCA2, and SCA3. Linkage of SCA3 to chromosome 14q was found in two French families using an array of markers spanning the MJD region.²⁴ For the markers D14S55 and D14S48, cumulative positive lod scores of 1.73 for a recombination fraction of 0.1 and 1.29 for a recombination fraction of 0.2 were obtained respectively. Thus, in agreement with our data, the SCA3 loci was found not to be tightly linked to either D14S55 or D14S48. From multilocus and haplotype analysis the predisposing SCA3 locus is thought to be located in a 15 cM interval flanked by the markers D14S68 and D14S81. Since MJD and SCA3 have been localised to the same region of chromosome 14 by linkage analysis it is possible that these two disorders are allelic. This hypothesis is further supported by the clinical similarity between the two diseases. From a study by Stevanin *et al.*,²⁴ the mean age of onset and the mean disease duration was shown to be similar between a group of 18 SCA3 patients and 12 MJD patients. In addition, the frequency of the cerebellar signs associated with cerebellar ataxia was not significantly different between the SCA3 patients and the MJD patients with the exception of faciolingual myokymia which was always present in MJD but never in SCA3, and dystonia which was significantly more frequent in MJD compared to SCA3 ($p < 0.05$). However, the clinical symptoms of SCA3 more closely resemble those of SCA1,²⁴ the locus of which is known to be on chromosome 6,³⁹ suggesting that clinical similarity is not necessarily indicative of genetic homogeneity.

A third autosomal dominant neurodegenerative disease, dentatorubropallidolusian atrophy (DRPLA) has recently been reported to be linked to chromosome 14q24.3-qter.⁴⁰ However, two independent reports have recently identified an expanded unstable CAG repeat on chromosome 12p in DRPLA patients from Japan,^{41,42} a finding which has recently been confirmed in a British DRPLA kindred.⁴³ Thus, it is possible that there are two genes responsible for DRPLA located on different chromosomes, although it is more probable that the chromosome 14 linked DRPLA is in fact MJD.

In conclusion, we have shown linkage of MJD to chromosome 14q in six American families of Portuguese/Azorean descent and in one Brazilian family indicating that MJD segregating in these families is the same as MJD described in Japan. In addition we have narrowed the region of chromosome 14q containing the MJD gene locus from 29 cM to 11 cM, an interval which maps within the re-

gion of chromosome 14q containing the SCA3 locus.

We would like to thank the families for their willingness to participate in this study and Drs B White and J Holden for assistance with lymphoblastoid transformation of cell lines from several American kindreds. We would also like to thank Dr S Marc for information regarding the marker AFM343v1. Elspeth C Twist is the holder of a Unisource Canada/Alzheimer Society of Canada/MRC fellowship award, Lindsay A Farrer was supported by a fellowship from the Sloan Foundation, and Guy A Rouleau is supported by the Medical Research Council of Canada and the Fonds de Recherches en Sante du Quebec and the National Institute of Health.

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