

Refinement of a locus for autosomal dominant hereditary motor and sensory neuropathy with proximal dominance (HMSN-P) and genetic heterogeneity

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Abstract Hereditary motor and sensory neuropathy with proximal dominance (HMSN-P) is an adult-onset peripheral neurodegenerative disorder which has been reported only in the Okinawa Islands, Japan. The disease locus of “Okinawa-type” HMSN-P has been previously mapped to 3q13.1, with all affected individuals sharing an identical haplotype around the locus, suggesting that the undiscovered causative mutation in HMSN-P originated from a single founder. We have newly found two large families from the western part of Japan within which multiple members developed symptoms similar to those exhibited by HMSN-P patients from Okinawa, with no record of

affinal connection between the islands. Using these pedigrees with “Kansai-type” HMSN-P, we carried out a linkage study utilizing eight microsatellite markers and identified a candidate region on 3q13.1 cosegregating with the disease (maximum two-point LOD score of 8.44 at $\theta = 0.0$) overlapping with the Okinawa-type HMSN-P locus. However, the disease haplotype shared among all affected members in these families was different from that in the Okinawa kindred, suggesting allelic heterogeneity. Such allelic variation should aid in the identification of the disease-causative gene. Moreover, the allelic heterogeneity of HMSN-P in the Japanese population suggests that HMSN-P may be more common across other ethnic groups, but classified into other disease categories.

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Introduction

Hereditary motor and sensory neuropathy with proximal dominance (HMSN-P) was first reported by Takashima et al. (1997) as an autosomal dominant form of hereditary motor and sensory neuropathy with dominant proximal involvement (MIM 604484). It was characterized by autosomal dominant inheritance, slowly progressive proximal neurogenic atrophy and weakness, and sensory disturbance such as paresthesia and vibration loss, leading to bedridden incapacity. Neuropathological examination revealed a decrease in the number of anterior horn cells and

marked loss of myelinated fibers in the posterior funiculus. The disease locus underlying HMSN-P was mapped to 3p14.1-q13 with LOD scores 4.04 and 3.10 at D3S1284 and D3S1591, respectively (Takashima et al. 1997). The subsequent fine mapping narrowed the candidate region to a 3.1 cM interval between D3S1591 and D3S1281, which certainly lies on 3q13.1, and the existence of a single founder was also suggested by information about shared marker alleles among patients and the geographical specificity of the disease (Takashima et al. 1999). The same group has recently refined the candidate region for HMSN-P in the coordinate system of the human genomic DNA sequence (H. Takashima et al. unpublished data).

Since HMSN-P was found in Okinawa, Japan, this disease has been regarded as having clinical features resembling those of Kennedy syndrome (MIM 313200), with the addition of an autosomal mode of inheritance; it is sometimes referred to as a part of the spectrum of Charcot–Marie–Tooth disease (CMT2P) (Gemignani and Marbini 2001). Thus far, however, HMSN-P has not been reported in other areas in the world. Recently, we newly found two large families with multiple affected members developing symptoms similar to those of HMSN-P in a small mountain village in the Kansai area of the mainland of Japan. Detailed electrophysiological and electromyography (EMG) examinations suggest that the disease is neurogenic as seen in HMSN-P found in Okinawa (Materials and methods). Moreover, neuropathological examination revealed extensive neuronal loss in the anterior horn of the spinal cord. Thus, we refer to the disease as the “Kansai-type” HMSN-P and the original HMSN-P in Okinawa as the “Okinawa-type.”

Although we did not find any clinical heterogeneities and inconsistency of the mode of inheritance between the Kansai-type and Okinawa-type, there was no record of immigration from Okinawa to the western village (or vice versa) or affinal connection between them. This poses a question about the genetic heterogeneity, namely, a question whether the disease locus of the Kansai-type overlaps with that of the Okinawa-type. Therefore, to identify the disease locus for the Kansai-type, we decided to begin by examining linkage of the Kansai-type HMSN-P with eight microsatellite markers covering the candidate locus (3q13.1) for Okinawa-type. We report the results of linkage analysis and of the identification of a disease haplotype shared among affected members in the pedigrees studied.

Materials and methods

Families and clinical features

Two large families with affected individuals were located in the Kansai area, ~1,200 km from Okinawa (Fig. 1).

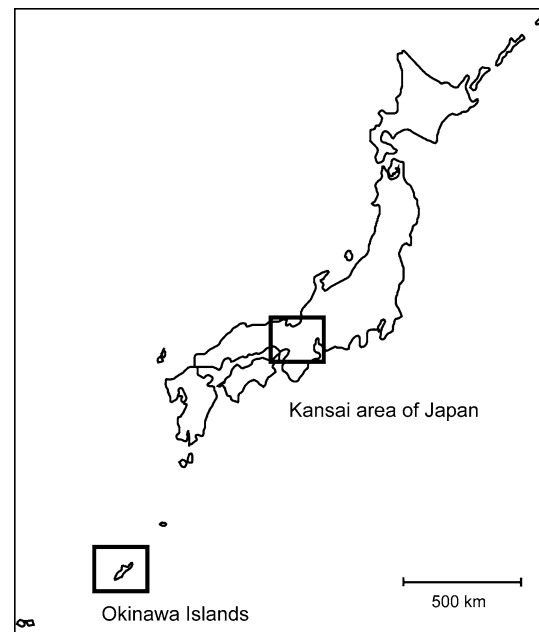


Fig. 1 Geographic distributions of the two types of HMSN-P in Japan. The two parts are 1,200 km from each other, separated by the sea. Thus far, in the small mountain village in the western part of Japan, no other family with the disease has been found

These families consist of 5–6 generations including at least 40 affected members (Fig. 2). The inheritance pattern of the disease in the pedigrees exhibits an autosomal dominant mode of inheritance (Fig. 2). Moreover, this disease showed no obvious clinical heterogeneity with the HMSN-P in Okinawa (Table 1), which shows malignant fasciculation associated with a disease process affecting peripheral motor nerves. Electrophysiological evaluation, including a nerve conduction study and EMG in the upper and lower extremities, revealed that compound muscle action potential (CMAP) amplitudes decreased while conduction velocities remained relatively intact and that sensory nerve action potential (SNAP) amplitudes also decreased or were absent due to involvement of the dorsal root ganglia. Examination via electromyography of affected muscles revealed prominent spontaneous activity, in the form of fibrillation potentials and positive sharp waves. Decreased recruitment of motor unit action potentials (MUAPs) with high amplitude and long-duration motor units was observed, evidence of prior axonal loss.

Subjects, DNA extraction, and microsatellite typing

A total of 16 affected and 31 unaffected members from the two families with HMSN-P in a mountain village participated in this study. In order to compare the disease haplotypes of the Kansai-type with Okinawa-type HMSN-P cases, we also genotyped an affected Okinawa kindred

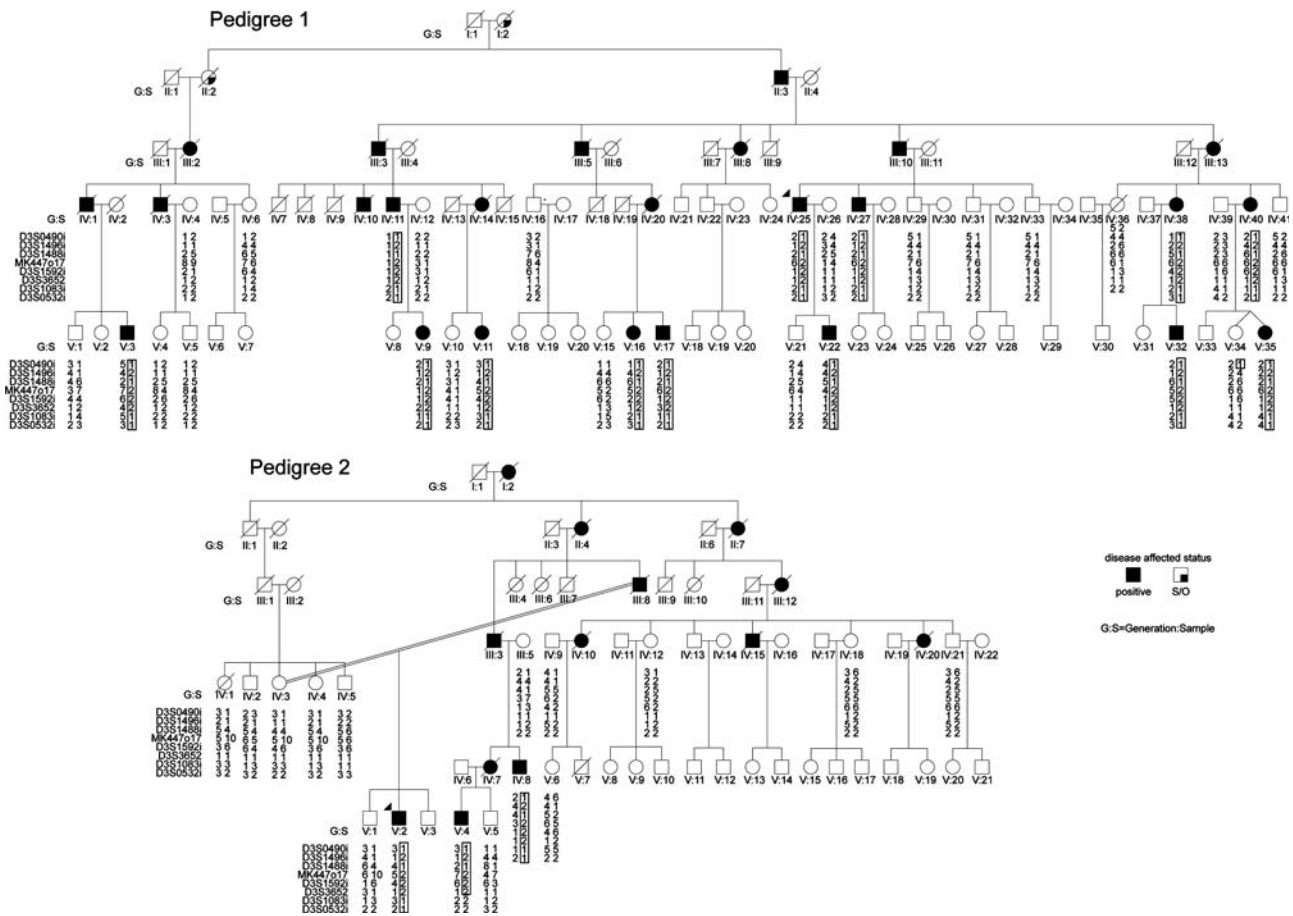


Fig. 2 Two large pedigrees with “Kansai-type” HMSN-P

sib-pair. Informed consent was obtained from all patients and healthy volunteers, and the study was approved by all of the participating institutes. Genomic DNA was extracted from lymphocytes of peripheral blood using a QIAamp DNA Blood Maxi Kit (Qiagen, Valencia, CA, USA) as per the manufacturer’s instructions. Hereafter, we will refer to each individual member using the corresponding identifier of Pedigree:Generation:Sample in Fig. 2. Of eight microsatellite markers, seven were selected around 3q13.1 from the GDBS database (<http://jbirc.jbic.or.jp/gdbs/top.jsp>) (Tamiya et al. 2005), and one was novel. We genotyped the eight markers for linkage analyses on the ABI3700 and all the information regarding these microsatellite makers is listed in Table 2. In order to refine a position of obligate recombination observed in Pedigree 1, we also examined four additional microsatellite markers between D3S0490i and D3S1496i. We also carried out confirmatory examination for D3S1291 (5′-TTT AAC AAT CCC AAT CAG G-3′ for forward primer and 5′-GGC AAA ATG TCT GCT GTA-3′ for reverse primer) in a few members in the Kansai-type families. The genotype data at D3S1291 in Okinawa-type patients was compiled from the previous works (Takashima

et al. 1997, 1999). The PCR condition and fragment analysis were according to a standard procedure described previously (Tamiya et al. 2005).

Linkage and haplotype analysis

We used eight microsatellite markers located on the chromosomal region 3p12-q13 (Fig. 3, Table 2). Since genetic map positions for all markers except D3S3652 had not been described, we extrapolated sex-averaged map positions for each such marker linearly using the nearest flanking microsatellite markers from the deCODE map (Kong et al. 2002). Mendelian segregation of marker genotypes was confirmed using the “Pedigree Check” program in Pedtool (Fishelson and Geiger 2002). Parametric two-point linkage analysis was performed using SUPERLINK-ONLINE (<http://bioinfo.cs.technion.ac.il/superlink-online/>) (Fishelson and Geiger 2002; Silberstein et al. 2006). Disease inheritance was assumed to be autosomal dominant with complete penetrance and without phenocopy. We assumed the disease allele frequency to be 0.0001 following the previous study (Takashima et al.

Table 1 Clinical information on patients with Kansai-type and Okinawa-type HMSN-P

	Kansai patients	Okinawa patients
Age of onset	37.5 ± 8 (men 42.0 women 42.0)	39.2 ± 9.0 (men 43.3 women 36.5)
Bedridden	10–20 years after disease onset	10–25 years after disease onset
Motor disturbance		
Gradual progression	+	+
Proximal muscle weakness and atrophy	+	+
Painful muscle cramp	+	+
Prominent fasciculation in the early stage	+	+
Loss of deep tendon reflex	+	+
Tetraplegia in advanced disease	+	+
Sensory disturbance		
Dysesthesia in distal limbs	+	+
Mild loss of touch and temperature	+	+
Severe loss of position and vibration sense	+	+
Other examinations		
Hyperglycemia	4 persons in 13 patients	16 persons in 39 patients
Hyperlipidemia	3 persons in 13 patients	11 persons in 39 patients
Creatine kinase	270 ± 101 IU L ⁻¹	301 ± 243 IU L ⁻¹
Spinal fluid	Normal	Normal
Brain and spinal cord MRI	Normal	Normal
Nerve conduction study	Motor and sensory axonal degeneration	Motor and sensory axonal degeneration
Needle EMG	Fibrillation potentials and positive sharp waves	Fibrillation potentials and positive sharp waves
Pathology	Loss of axons in peripheral nerves, anterior horn cells, and dorsal root ganglion cells	Loss of axons in peripheral nerves, anterior horn cells, and dorsal root ganglion cells

1997). For marker alleles, we assumed equal allele frequencies at each locus.

Results

Two-point LOD scores are shown in Table 3. In Pedigree 1, six of the eight-microsatellite markers showed significant LOD scores (LOD > 3.3) exhibiting evidence of linkage of the 3p12-q13 region to the Kansai-type HMSN-P and the Okinawa-type. The maximum LOD scores for the two pedigrees were 6.72 in Pedigree 1 and 1.72 in Pedigree 2, obtained at the same marker D3S1592i with zero recombination fraction, $\theta = 0$. Combining two pedigrees, we see that five markers from D3S1496i to D3S3652 showed the clear evidence of linkage to the Kansai-type HMSN-P (Table 3).

To infer a disease haplotype (i.e., a haplotype cosegregating with disease) based upon the evidence of linkage,

we assume that if there is more than one possible diplotype configuration, a configuration with a minimum number of recombination events is more likely. We abbreviate this assumption to the MREC (minimum recombination events configuration). This assumption may be appropriate for our data with short marker distances and is analogous to the minimum recombinant haplotype configurations in the pedigree considered in Qian and Beckmann (2002). Inspecting nuclear families with affected offspring 1:V:9, 1:V:22, and 1:V:35 for which both parents were genotyped, we find that an eight-marker haplotype inherited from their affected parents is 121222[1]1, where [1] at D3S1083i stands for ambiguity in 1:V:22 under the MREC assumption (Fig. 2). Note here that an obligate recombination between D3S0490i and D3S1496i is observed for an inheritance from an affected parent 1:IV:40 to either of dizygotic twins 1:V:34 or 1:V:35, which resulted in the LOD score of minus infinity at D3S0490i (Table 3). This means that the linkage of D3S0490i to the disease is

Table 2 Information on the microsatellite marker on chromosome 3p12.2–3q13.11 for linkage analysis

Maker name	PCR primers		Reverse	Map position		Number of alleles	HET ^d	PIC ^e
	Forward			Chromosome band ^a	deCODE map ^b (cM)			
D3S0490i	TTGTATCAAAGCATCTTGTA		GCCTAATAATTTGTTCTCCAAC	3p12.2	107.57	6	0.80	0.77
D3S1496i	TGCTAGCTGAGTATTTGCACAC		TGAGGTGGGAGATTCATTAC	3p12.1	110.09	4	0.64	0.58
D3S1488i	CTTAGGCTCCTTAAATTCACAC		TGGATAATTAGGTCAGAGCTATC	3q11.1–12.1	111.45	8	0.85	0.83
MK447o17	CATCAGAACAGCAACATTCAC		TGGATCAGATGACCTCCAITT	3q11.1–12.1	111.82	10	0.85	0.83
D3S1592i	CCTCATTTAAAGGACATACTTCAC		AGGTGGTATGCCTCTATTGTTAG	3q11.2–12.1	111.97	6	0.80	0.77
D3S3652	GAAAAAATAGTCTCCAGTCAAGTAGC		ATGCCCATCAATCAATGAGT	3q12.2	113.38	4	0.44	0.38
D3S1083i	CAGTTGCACATGGAGTATAAATC		GATCAACTCCTGTAGATTCTACAG	3q13.11	115.07	5	0.68	0.64
D3S0532i	GTAAACAATCTTGTGCATCAAG		AGTTAACTACTGTTACTTTGGCCTC	3q13.11	115.67	4	0.53	0.44

^a Inferred from flanking markers in deCODE map

^b Linearly interpolated using the nearest flanking markers in deCODE map

^c NCBI build 35

^d Heterozygosity estimated from allele frequencies estimated from 95 unrelated subjects

^e Polymorphism information content estimated as in d

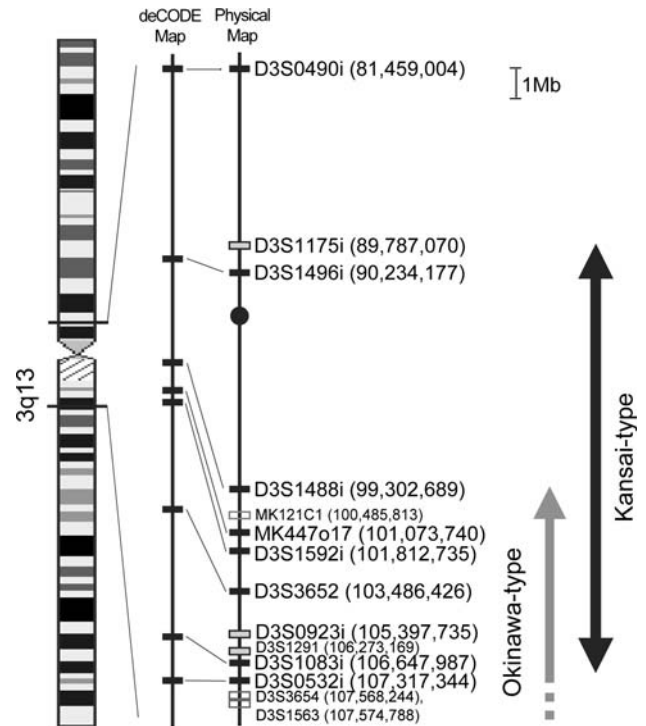


Fig. 3 The intervals co-segregated with the Kansai-type and Okinawa-type of HMSN-P. The genetic distances were linearly interpolated using the nearest flanking markers in the deCODE map. Physical distances were calculated from the coordinate system of the human genomic DNA sequence in NCBI build 35. *Black boxes* in the map bars represent microsatellite markers used in the linkage analysis. *Gray boxes* represent markers for additional typing. *Open boxes* represent markers used in previous work (Takashima et al. 1997, 1999). The *closed circle* indicates the centromere

rejected, so we consider only the remaining seven markers: a candidate disease haplotype is 21222[1]1 from D3S1496i to D3S0532i. Under the MREC assumption, all the affected members in Pedigree 1 may share the same haplotype 21222[1]1 without introducing any additional recombinations in the pedigree (Fig. 2). In Pedigree 2, only one affected member 2:V:4 cannot have this haplotype for the terminal 2 markers (D3S1083i and D3S0532i), resulting in the exclusion of linkage for these markers (Table 3). For the remaining affected members 2:IV:8 and 2:V:2, the seven-marker disease haplotype is 2[1]22211, where [1] at D3S1496i indicates ambiguity in 2:IV:8. Thus, under the MREC assumption, we identify a unique five-marker (from D3S1496i to D3S3652) haplotype 2[1]222 cosegregated with disease and shared by all the affected members of both pedigrees.

We summarize the result of additional genotyping with genotype results for affected siblings of Okinawa-type in Table 4. It is evident that a recombination occurred between D3S0490i and D3S1048i in the inheritance from 1:IV:40 to 1:V:34. The location of this event depends on the paternal allele of 1:V:35 at D3S1070i.

Table 3 Two-point LOD scores between phenotype and markers on chromosome 3p12.2–3q13.11

Marker Name	Map position deCODE ^a (cM)	Recombination fraction (genetic distance)										
		0.00 (0.0 cM)	0.01 (1.0 cM)	0.05 (5.3 cM)	0.10 (11.2 cM)	0.20 (25.5 cM)	0.30 (45.8 cM)	0.40 (80.5 cM)				
Pedigree 1												
D3S0490i	107.57	-Infinity	0.56	1.09	1.14	0.87	0.50	0.20				
D3S1496i	110.09	5.41	5.30	4.83	4.20	2.90	1.61	0.49				
D3S1488i	111.45	4.59	4.47	3.97	3.35	2.19	1.23	0.50				
MK447o17	111.82	5.28	5.21	4.86	4.29	3.02	1.71	0.53				
D3S1592i	111.97	6.72	6.57	5.95	5.17	3.65	2.18	0.76				
D3S3652	113.38	4.94	4.84	4.39	3.80	2.55	1.23	0.06				
D3S1083i	115.07	1.89	1.84	1.64	1.39	0.93	0.53	0.22				
D3S0532i	115.67	6.25	6.12	5.59	4.91	3.51	2.07	0.69				
Pedigree 2												
D3S0490i	107.57	-0.02	0.00	0.05	0.08	0.09	0.06	0.03				
D3S1496i	110.09	1.50	1.48	1.38	1.24	0.92	0.58	0.27				
D3S1488i	111.45	1.40	1.36	1.20	0.99	0.59	0.26	0.04				
MK447o17	111.82	1.19	1.20	1.19	1.08	0.74	0.38	0.12				
D3S1592i	111.97	1.72	1.72	1.67	1.52	1.12	0.68	0.28				
D3S3652	113.38	1.64	1.60	1.45	1.26	0.87	0.50	0.19				
D3S1083i	115.07	-Infinity	-1.85	-1.06	-0.70	-0.38	-0.22	-0.10				
D3S0532i	115.67	-Infinity	-0.63	-0.11	-0.02	-0.09	-0.15	-0.12				
Combined												
D3S0490i	107.57	-Infinity	0.56	1.15	1.22	0.96	0.57	0.23				
D3S1496i	110.09	6.92	6.78	6.21	5.44	3.82	2.19	0.76				
D3S1488i	111.45	6.00	5.83	5.17	4.34	2.78	1.49	0.54				
MK447o17	111.82	6.46	6.42	6.04	5.37	3.76	2.10	0.65				
D3S1592i	111.97	8.44	8.29	7.62	6.70	4.77	2.86	1.04				
D3S3652	113.38	6.58	6.44	5.85	5.06	3.41	1.73	0.26				
D3S1083i	115.07	-Infinity	-0.02	0.58	0.69	0.54	0.31	0.12				
D3S0532i	115.67	-Infinity	5.49	5.49	4.89	3.42	1.92	0.57				

^a Linearly interpolated using the nearest flanking markers in deCODE map

Table 4 Inference of disease haplotype and additional genotyping result

No.	Marker name ^a	Physical distance (bp)	Disease haplotype ^b	Kansai-type ^c										Okinawa-type	
				1:IV:11 Aff	1:IV:12 Unaff	1:V:9 Aff	1:IV:25 Aff	1:IV:26 Unaff	1:V:22 Aff	1:IV:39 Unaff	1:IV:40 Aff	1:V:34 Unaff	1:V:35 Aff	Patient 1	Patient 2
			Paternal or Maternal			P M			P M			P M	P M		
1	* D3S0490i	81,459,004	x	1 1	2 2	1 2	2 1	4 2	1 4	(2 3)	(2 1)	2 1	2 1	4 / 2	4 / 2
3	D3S1070i	83,636,724	2	1 2	3 2	2 2	2 2	1 1	2 1	(1 2)	(1 2)	1 1	(1 2)	- / -	- / -
4	D3S0780i	84,751,517	1	1 1	5 1	1 1	1 1	1 1	1 1	(1 3)	1 1	1 1	3 1	- / -	- / -
6	D3S0528i	85,662,562	2	3 2	3 6	2 6	1 2	5 5	2 5	1 1	2 2	1 2	1 2	- / -	- / -
9	D3S1048i	90,118,879	2	4 2	4 3	2 3	1 2	1 3	2 1	4 4	3 2	4 3	4 2	- / -	- / -
10	* D3S1496i	90,234,177	2	1 2	1 1	2 1	1 2	4 3	2 4	2 3	4 2	2 4	2 2	4 / 1	4 / 1
11	* D3S1488i	99,302,689	1	1 1	2 2	1 2	2 1	5 2	1 5	2 3	6 1	2 6	2 1	6 / 7	2 / 7
12	* MK447o17	101,073,740	2	1 2	3 1	2 1	6 2	4 1	2 4	6 6	6 2	6 6	6 2	5 / 6	7 / 6
13	* D3S1592i	101,812,735	2	1 2	3 1	2 1	1 2	1 1	2 1	1 6	6 2	1 6	1 2	1 / 4	6 / 4
14	* D3S3652	103,486,426	2	1 2	1 2	2 2	1 2	1 1	2 1	1 1	1 2	1 1	1 2	1 / 1	1 / 1
22	* D3S1083i	106,647,987	x	2 1	2 1	1 1	(2 1)	(2 1)	(1 2)	4 1	1 1	4 1	4 1	2 / 1	2 / 1
23	* D3S0532i	107,317,344	x	2 1	2 2	1 2	2 1	2 3	1 2	4 2	2 1	4 2	4 1	2 / 2	3 / 2

Aff affected, Unaff unaffected

^a Microsatellite makers used in the linkage analysis were indicated by asterisk. Hyphen indicates “not examined”

^b The disease haplotype was inferred as described in the text

^c Brackets indicate the ambiguity in the phase. Dashed box stands for the location of recombination which cannot be refined any more

Discussion

In this study, we demonstrated that the disease locus for the Kansai-type HMSN-P is strongly linked to 3q13, overlapping with a region previously assigned as a candidate locus for Okinawa-type HMSN-P (Takashima et al. 1999). This coincidence of the disease locus might reflect the clinical overlap of the two diseases. The coincidence of the disease locus and the clinical homogeneity suggest that the causative gene for both types is identical and is located within the 7.3 Mb interval between D3S1488i and D3S1083i (Fig. 3), which includes at least 21 known genes from *FLJ35799* to *ZPLD1*. Our result from the linkage analysis warrants further study, such as an extensive mutation search in expressed genes including these known genes within this interval that co-segregate with the disease.

The existence of a unique disease haplotype shared among all the affected members in the two western families is suggestive of a founder mutation in the western population, as with the case of Okinawa-type (Takashima et al. 1997). It seems, however, that disease haplotypes are not shared between the two types (Table 4). Of four microsatellite markers used in previous works (Takashima et al. 1997, 1999), the precise position of A281WA5 in the coordinate system of the human genomic sequence was never determined, i.e., was unmapped. On the other hand, D3S3654 and D3S1563 did not locate within the interval linked to the Kansai-type HMSN-P (Fig. 3). The disease alleles at D3S1291 in the linked interval seem to be different between Kansai-type (186 in size) and Okinawa-type

(188 from the previous works by Takashima et al.), which is consistent with our finding. Such a circumstance is not unusual when the same locus is linked to the disease for different pedigrees. Therefore, the allelic heterogeneity is suggested in the two types of HMSN-P that share the same disease locus, as is often the case for rare Mendelian diseases. We also note that, although HMSN-P has been reported only in Japan, there is a possibility that HMSN-P has already been found in other areas in the world but has been erroneously classified into other disease categories, such as hereditary motor neuropathy (HMN), spinal muscular atrophy (SMA), limb-girdle muscular dystrophy (LGMD), or amyotrophic lateral sclerosis (ALS). Although HMN, SMA, LGMD, and ALS are also progressive muscular atrophic diseases, these diseases do not involve the sensory system primarily. On the other hand, HMSN-P involves peripheral sensory nerves severely when the disease progresses. Diagnosis of HMSN-P is based on existing sensory nerve disturbance both subjectively, and objectively by EMG examination, in addition to proximal dominant muscular atrophy. Until a specific genetic test is available, this hypothesis can be verified by a confirmatory screen using electrophysiological examination in patients with these diseases. The confirmatory screening of the allelic heterogeneity of HMSN-P will be important to facilitate identification of the causative gene and investigation of the gene function in the same scenario as CMT2F and distal HMNs (Evgrafov et al. 2004).

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