Hereditary neuropathy
CMT and HMSN-P

on 5th. August, 7:30 to 8:30, Multidisciplinary Pain Group.

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Professor and chairman
Department of Neurology,
Graduate School of Medical Science,
Kyoto Prefectural University of Medicine, Kyoto, Japan

The overseas scientific research for the elucidation of the mechanism of a novel hereditary motor sensory neuropathy originated in Japan
This work is supported by a Grant-in-Aid for Scientific Research (B) from JSPS (21406026).
: JSPS KAKENHI (21406026)
関西空港
Seattle
Milwaukee
Sao Paulo
Atlanta

7月31日～8月7日
Charcot-Marie-Tooth disease (CMT) is the most commonly inherited peripheral neuropathy and is found worldwide among all races and ethnic groups. Discovered in 1886 by three physicians, Jean-Martin Charcot, Pierre Marie, and Howard Henry Tooth, CMT affects an estimated 2.6 million people.
Clinical presentation of CMT

The disease onset usually occurs in the first two decades of life and subsequently shows a slow progression over decades. Symptoms and signs indicative of CMT include: pes cavus (or pes planus); hammer toes; difficulty in running; twisting of the ankle and tripping; difficulty in walking; foot drop; steppage gait; wasting, weakness, and sensory loss of distal segments of lower and then upper limbs; difficulties in hand manipulation; and reduced or absent deep-tendon reflexes. Other common symptoms and signs are hand tremors, muscle cramps, cold feet, foot callosities, acrocyanosis and pain.

The uncommon associated features such as involvement of cranial nerves, vocal cord palsy, pupillary abnormalities, glaucoma, optic atrophy, pyramidal involvement, predominant upper-limb involvement, prominent sensory abnormalities, and proximal dominant involvement.
CMT1

CMT (Intermediate forms)

CMT2

**Intermediate CMT**: unable to classify by 38m/sec, DI-CMT, RI-CMT

**NCV in median nerve**: 38m/sec

Demyelination CMT

CMT1(AD), CMT4(AR)

Axonal CMT

CMT2 (AD, AR)

- **CMT X**
- **DI-CMT**
- **RI-CMT**
- **CMT 2**
- **CMT1A**

**CMAP**: almost normal or slightly delayed

**Segemental demyelination**

**Onion bulb formation**

**CMAP**: markedly reduced

**Decreased myelinated fiber density**
Genes and loci of Inherited Peripheral Neuropathies

About 50 loci and 40 genes have been identified
Node of Ranvier

Axon

compact myelin

Basal lamina

Schwann Cell

Microtubule

Mitochondria

KIF1B

NEFL

GAN

Laminin

DAG1

DRP2

PRX

Schmidt-Lantermann Incisure

PMP22

Cx32

PRX

MPZ

NDRG1

SOX10

MFN2

MTMR13

EGR2

Different forms of CMT disease and associated genes

Lancet Neurol 2009; 8: 654–67
Genetic classification of CMT

CMT

CMT1

AD

AR

X-linked

PMP22

MPZ

LITAF

EGR2

NEFL

GDAP1

MTMR2

MTMR13

SH3TC2

NDGR1

EGR2

PRX

HK1

FGD4

FIG4

CTDP1

PMP22

MPZ

GJB1

KIF1B

MFN2

RAB7

TRPV4

GARS

NEFL

HSPB1

HSPB8

MPZ

AARS

GDAP1

CMT2

AD

AR

X-linked

LMNA

MED25

GDAP1

NEFL

MFN2

HSPB1

PRPS1

Intermediate CMT

AD

AR

DNM2

YARS

GJB1

NEFL

MPZ

GDAP1

AD

AR

X-linked

CMT

脱髓型（CMT1）
- AD
  - PMP22
  - MPZ
  - LITAF
  - EGR2
  - NEFL
- AR
  - GDAP1
  - MTMR2
  - MTMR13
  - SH3TC2
  - NDGR1
  - EGR2
  - PRX
  - HK1
  - FGD4
  - FIG4
  - CTDP1
  - PMP22
  - MPZ
- X-linked
  - GJB1

軸索型（CMT2）
- AD
  - KIF1B
  - MFN2
  - RAB7
  - TRPV4
  - GARS
  - NEFL
  - HSPB1
  - HSPB8
  - MPZ
  - AARS
  - GDAP1
- AR
  - LMNA
  - MED25
  - GDAP1
  - NEFL
  - MFN2
  - HSPB1
  - PRPS1
  - DNM2
  - YARS
  - GJB1
  - NEFL
  - MPZ
  - GDAP1

中間型（DI or RI CMT）
- AD
- AR
## Incidence of CMT related genes  in USA, Italy and Japan

### Gene mutations in demyelinating CMT

<table>
<thead>
<tr>
<th></th>
<th>PMP22 duplication</th>
<th>PMP22</th>
<th>MPZ</th>
<th>LITAF</th>
<th>NEFL</th>
<th>GJB1</th>
<th>GDAP1</th>
<th>MTMR2</th>
<th>MTMR13</th>
<th>EGR2</th>
<th>PRX</th>
<th>DNMT2</th>
<th>YARS</th>
<th>Unknown</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Japan</td>
<td>53 (23.3%)</td>
<td>10 (4.4%)</td>
<td>20 (8.8%)</td>
<td>0 (0%)</td>
<td>8 (3.5%)</td>
<td>19 (8.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (0.4%)</td>
<td>5 (2.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>111 (48.9%)</td>
<td>227</td>
</tr>
<tr>
<td>Italy</td>
<td>98 (57.6%)</td>
<td>2 (1.2%)</td>
<td>4 (2.3%)</td>
<td>N.D.</td>
<td>N.D.</td>
<td>12 (7.1%)</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>54 (31.8%)</td>
<td>170</td>
</tr>
<tr>
<td>USA</td>
<td>79 (54.1%)</td>
<td>5 (3.4%)</td>
<td>5 (3.4%)</td>
<td>N.D.</td>
<td>N.D.</td>
<td>8 (5.5%)</td>
<td>0 (0%)</td>
<td>N.D.</td>
<td>N.D.</td>
<td>1 (0.7%)</td>
<td>1 (0.7%)</td>
<td>N.D.</td>
<td>N.D.</td>
<td>51 (34.9%)</td>
<td>146</td>
</tr>
</tbody>
</table>

PMP22 mutations include a compound heterozygote of a PMP22 deletion and a missense Arg157Gly mutation22 and a compound heterozygote of a PMP22 deletion and an exon 5 deletion mutation. N.D. not done.

Incidence of CMT related genes in USA and Japan

Gene mutations in axonal CMT

<table>
<thead>
<tr>
<th></th>
<th>MFN2</th>
<th>RAB7</th>
<th>GARS</th>
<th>NEFL</th>
<th>HSP27</th>
<th>MPZ</th>
<th>HSP22</th>
<th>GDAP1</th>
<th>GJB1</th>
<th>DNM2</th>
<th>YARS</th>
<th>Unknown</th>
<th>Total</th>
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<tbody>
<tr>
<td>Japan</td>
<td></td>
<td></td>
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<td>100</td>
<td>127</td>
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<tr>
<td></td>
<td>11.0%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>4.0%</td>
<td>4.0%</td>
<td>4.7%</td>
<td>4.7%</td>
<td>4.7%</td>
<td>4.7%</td>
<td>78.7%</td>
<td></td>
</tr>
<tr>
<td>USA (2011)</td>
<td>21</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>96</td>
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<tr>
<td></td>
<td>21.9%</td>
<td>0.8%</td>
<td>1.5%</td>
<td>4.2%</td>
<td>0.8%</td>
<td>4.0%</td>
<td>0.8%</td>
<td>2.6%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>65.6%</td>
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</table>

Commentary

A Commentary on Molecular diagnosis and clinical onset of Charcot–Marie–Tooth disease in Japan

Masanori Nakagawa

How can we ultimately identify the causative genes in the patients with unknown cause? What are the genetic and epigenetic modifying factors that potentially affect the phenotypic expression of the patients with PMP22 duplication? It could be helpful to establish a high-throughput screening method using the next-generation sequencer for identification of the causative gene of patients with unidentified mutations and the genetic and epigenetic modifying factors of CMT. In addition, molecular epidemiological study of CMT in Asian countries including Korea and China, where Japanese lineage may encroach, so as to provide more insights into the genetic background of the low prevalence of PMP22 duplication in Japan.
Known genes: 28 genes
Candidate genes: 11 genes
DNA Chip (resequencing chip) 110.938 bp on the chip

It is able to screen 28 genes and 11 candidate genes at once.
Genetic diagnosis system for hereditary neuropathy diagnosis
High throughput and low cost protocol

Multiplex PCR reaction

Pts DNA sample
no PMP22 duplication
CMT2

Roche GS Junior
Personal genome sequencer
40 million bp/8 hours

DNA chip for hereditary neuropathy diagnosis

Microarray analysis
Gene Chip Scanner 3000

PCR products
Pooled PCR (Max 548 reactions)

DNase I digestion

End-labeled fragments
Patients suspected of CMT

Clinical symptoms and electrophisiological evaluation

CMT2 excluded

PMP22 FISH or MLPA method

CMT2 confirmed

CMT1 A/HNPP

(Nerve biopsy if necessary)

Screening the causative gene

Gene analysis centers in Japan
$PMP22$ deletion/duplication detected by FISH

One copy of $PMP22$

HNPP

(Hereditary Neuropathy with liability to pressure palsies)

Two copies of $PMP22$

Normal

Three copies of $PMP22$

CMT1A

Fiber FISH
Patients suspected of CMT

Clinical symptoms and electrophisiological evaluation

CMT2 excluded

PMP22 FISH or MLPA method

CMT2 confirmed

CMT1 A/HNPP

(Nerve biopsy if necessary)

Screening the causative gene

Gene analysis centers in Japan

Kagoshima University, Prof. Takashima is organizing
cmtdiag@m3.kufm.kagoshima-u.ac.jp
Autosomal dominant hereditary motor and sensory neuropathy with proximal dominancy (HMSN-P)
HMSN-P is an autosomal dominant slowly progressive neuromuscular disease that we first described in patients from Okinawa, a southern archipelago in Japan. The clinical features of HMSN-P include proximal dominant neurogenic atrophy with fasciculations, painful muscle cramp, sensory involvement, and areflexia. The serum level of creatine kinase is elevated and the patients have a higher incidence of hyperlipidemia and diabetes mellitus. The electrophysiological findings are consistent with motor and sensory axonal neuropathy. In neuropathology, the number of anterior horn cells and dorsal root ganglion cells markedly decreased, suggesting that the sensorimotor neuronopathy is the cardinal feature in HMSN-P (Ann Neurol 41: 771, 1997). We have mapped the gene locus to chromosome 3p14.2-3q13. The presence of a common allele of marker D3S1591 and the geographical specificity of the disease suggested the presence of linkage disequilibrium and a single founder of this disease.
Okinawa
HMSN-P is a slowly progressive intractable disease and some patients eventually require a tracheotomy with artificial ventilation, mimicking the clinical course of familial amyotrophic lateral sclerosis (FALS). It is thus no wonder that preexisting diagnoses in patients with HMSN-P include FALS, adult-onset spinal muscular atrophy (SMA), or Charcot-Marie-Tooth disease type 2 (CMT2). When a patient with HMSN-P is diagnosed, the disease has often been transmitted to the next generation because HMSN-P is essentially an adult-onset autosomal dominant disorder. Genetic counseling is, therefore, crucial.

The gene locus of HMSN-P has been mapped to an overlapping centromeric region on chromosome 3 in two independent linkage analyses, one from Okinawa family and another family reported in Shiga prefecture in mainland Honshu, Japan.
Clinical and pathological features in HMSN-P

1) Adult onset slowly progressive proximal dominant neurogenic atrophy
   Mean ages of disease onset are 43.3 y.o. in men and 36.5 y.o. in women.
2) Obvious sensory involvement and areflexia
   Areflexia was present in the very early stage of disease in all patients.
3) Painful muscle cramp and fasciculations
4) High incidences of elevated creatine kinase levels, diabetes mellitus
   and hyperlipidemia
5) Electrophysiological evidence of axonal degeneration in peripheral
   nerves
   Needle EMG revealed fasciculation and fibrillation potentials and
   neuromyotonic signs in the early stage of the disease.
6) Markedly decreased anterior horn cells and loss of myelinated fibers in
   the posterior funiculus and peripheral nerves
7) Autosomal dominant inheritance
   More than 100 patients with HMSN-P, 8/10^5 population, are estimated in Okinawa.
More than 100 patients with HMSN-P, 8/10^5 population, are estimated in Okinawa by our epidemiological study. Only 7 of 18 families with HMSN-P are shown in this figure.
Autoradiogram of alleles of DNA marker D3S1591 in 20 patients with HMSN-P and 20 unrelated normal controls. Allele 6 was present in all 20 patients in contrast to only 6 of 20 controls.
A New Type of Hereditary Motor and Sensory Neuropathy Linked to Chromosome 3

Hiroshi Takashima, MD,*† Masanori Nakagawa, MD,* Keiichi Nakahara, MD,* Masahito Suehara, MD,* Toshio Matsuzaki, MD,*† Itsuro Higuchi, MD,* Hidemasa Higa, MD,† Kimiyoshi Arimura, MD,* Teruo Iwamasa, MD,§ Shuji Izumo, MD,‖ and Mitsuhiro Osame, MD*

We report the clinical, pathological, and genetic findings of 23 patients in 8 families with hereditary motor and sensory neuropathy (proximal dominant form) (HMSN-P) in Okinawa, Japan. The clinical features were unique with respect to autosomal dominant inheritance, Kennedy-Atler-Sung syndrome-like proximal dominant neurogenic atrophy, obvious sensory involvement, painful muscle cramp, fasciculations, areflexia, and high incidences of elevated creatine kinase levels, hyperlipidemia, and diabetes mellitus. Electrophysiological and pathological studies revealed typical motor and sensory axonal neuropathy, and decreased numbers of anterior horn and dorsal ganglion cells, which suggested the presence of neuronopathy in HMSN-P. Genetic linkage studies showed a lod score of 4.04 (two-point analysis) in DNA marker D3S1284. Haplotype analysis showed that the gene locus of the disease was mapped to 3p14.1-q13 bracketed by D3S1285 and D3S1281. In this region, the patients' chromosomes showed an obvious increase in the allele frequency of five markers. One allele in D3S1591 was identical in all patients but had a low frequency in the control population. This finding suggested the presence of linkage disequilibrium and a common origin of this allele in all patients with HMSN-P. The HMSN-P described here is a new clinical entity characterized by unique clinical manifestations and a new gene locus.

HMSN-P gene mapped to 3cM region at 3q13.1
by genetic linkage and linkage disequilibrium analysis

Takashima et al. (1997) reported ……………locus almost certainly lies on 3q13.1.
CREATION DATE  Victor A. McKusick : 1/31/2000

*604484
NEUROPATHY, HEREDITARY MOTOR AND SENSORY, OKINAWA TYPE:  HMSNO
HEREDITARY MOTOR AND SENSORY NEUROPATHY, PROXIMAL TYPE:  HMSNP

Gene Map Locus: 3q13.1

Takashima H, Nakagawa M, et al.
* Neuromuscul Disord 9: 368-371, 1999

Nakagawa M, Takashima H, et al.
* Ann NY Acad Sci 883: 449-452, 1999

Chromosome 3
Refinement of a locus for autosomal dominant hereditary motor and sensory neuropathy
With proximal dominancy (HMSN-P) and genetic heterogeneity
## Comparison between Okinawa and Kansai families

<table>
<thead>
<tr>
<th></th>
<th>Okinawa</th>
<th>Kansai</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of inheritance</td>
<td>AD</td>
<td>AD</td>
</tr>
<tr>
<td>Onset age (year)</td>
<td>39.2±9.0</td>
<td>37.5±8.0</td>
</tr>
<tr>
<td>Unable to walk (year)</td>
<td>56.9±6.2</td>
<td></td>
</tr>
<tr>
<td>Symptoms (symptoms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>slowly progressive</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>proximal dominant atrophy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>painful muscle cramp</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>fasciculations</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>areflexia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>sensory involvement</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Electrophysiological findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>motor and sensory axonal neuropathy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>highCKnemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>hyperlipidemia, and diabetes mellitus</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pathological findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>loss of myelinated fibers</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>decreased numbers of anterior horn and dorsal ganglion cells</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gene locus</td>
<td>3q12-13</td>
<td>3q13.1</td>
</tr>
</tbody>
</table>
Maeda et al. has recently reported a new case of HMSN-P in a Brazilian family with Japanese ancestry. It is interesting to note that Brazil has held huge immigrants from Japan since 1908, reaching eighteen million at present. In addition, more than one third of the initial Brazilian immigration came from Okinawa islands. The people from Okinawa prefecture have immigrated to American continents, including Brazil (approximately 130,000), United States (80,000), Peru (40,000), Argentina (30,000), Bolivia (10,000), Canada (1,500), and Mexico (650), and other countries (7,250). We can thus assume that HMSN-P is not only limited in Japan, but might have spread worldwide, especially in the countries which holds with many Okinawan immigrants.
Case series

Hereditary motor and sensory neuropathy (proximal dominant form, HMSN-P) among Brazilians of Japanese ancestry

Kengo Maeda\textsuperscript{a,}\textstar, Makoto Sugiura\textsuperscript{b}, Hiroko Kato\textsuperscript{b}, Mitsuru Sanada\textsuperscript{a}, Hiromichi Kawai\textsuperscript{a}, Hitoshi Yasuda\textsuperscript{a}

\textsuperscript{a} Division of Neurology, Department of Medicine, Shiga University of Medical Science, Seta-Tsukinowa, Otsu, Shiga 520-2192, Japan
\textsuperscript{b} Department of Neurology, Anjo Kosei Hospital, Anjo, Aichi 446-8002, Japan

Received 4 April 2007; received in revised form 22 July 2007; accepted 23 July 2007

Abstract

Hereditary motor and sensory neuropathy (proximal dominant form, HMSN-P) has been reported exclusively from Okinawa Prefecture in Japan. We herein report three brothers with HMSN-P who are among Brazilians of Japanese ancestry. They showed the typical clinical manifestations and were compatible with HMSN-P. Okinawa Prefecture has been a site of emigration to other countries, mainly in South America, since 1908. Although this is the first reported familial case of HMSN-P occurring outside Japan, it is estimated that there are 19 or 20 individuals with HMSN-P among these emigrants. Since HMSN-P might be misdiagnosed as familial amyotrophic lateral sclerosis or spinal muscular atrophy, neurologists in countries where individuals of Okinawan extraction reside should be aware of this hereditary neuropathy. HMSN-P should no longer be regarded as an endemic condition limited to Okinawa.

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Keywords: HMSN-P; Okinawa; Brazil; Immigrants
Case 1

A 42-year-old man

He was a second-generation descendent of immigrants of Okinawan origin whose residence was Brazil. His parents, born in Okinawa, had immigrated to Brazil in 1958. His father had walking difficulty since 40 years of age, had become bedridden, and died of respiratory disease at the age of 50. Our patient, born in Brazil, had noticed weakness of his shoulders at the age of 33. He also experienced difficulty in climbing stairs. Occasionally, he had painful muscle cramping in his abdominal muscles.

At age 38, he had been diagnosed as having spinal muscular atrophy based on neurogenic changes detected on electromyography and increased level of CK. Small grouped atrophy and fiber type grouping were found in biopsied muscle. However, nerve conduction study showed decreased amplitude of SNAP in the median, ulnar, and sural nerves.

Cranial nerves were normal, and the tongue was not atrophic. Weakness was pronounced in the proximal limbs. His deltoid muscles were atrophic. The MRC scale values were 3/3 (right/left) for the deltoid, 4/4 for the biceps and triceps, 5/5 for the wrist extensor and flexor, 4/4 for the iliopsoas, and 5/5 for the hip extensor, quadriceps femoris, hamstrings, anterior tibial, and gastrocnemius muscles. Fasciculation was found in the anterior chest muscles. Deep tendon reflexes were decreased. Vibratory sensations were slightly decreased in the digits of the hands and great toes. Superficial sensations were normal.
<table>
<thead>
<tr>
<th>Case</th>
<th>Age at onset</th>
<th>Median nerve</th>
<th>Tibial nerve</th>
<th>Sural nerve</th>
<th>CK (IU/l)</th>
<th>Cholesterol (mg/dl)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MCV (57.7 ± 4.9)</td>
<td>CMAP (7.0 ± 3.0)</td>
<td>SCV (56.2 ± 5.8)</td>
<td>SNAP (38.5 ± 15.6)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>57</td>
<td>6.6</td>
<td>54</td>
<td>2.0</td>
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<tr>
<td>2</td>
<td>46</td>
<td>54</td>
<td>8.6</td>
<td>56</td>
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<td>3</td>
<td>41</td>
<td>61</td>
<td>7.2</td>
<td>36</td>
<td>2.9</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>MCV (48.5 ± 3.6)</td>
<td>CMAP (5.8 ± 1.9)</td>
<td>SCV (52.5 ± 5.6)</td>
<td>SNAP (20.9 ± 8.0)</td>
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<td>49</td>
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<tr>
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<td>ND</td>
<td>ND</td>
<td>552</td>
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<td>4.6</td>
<td>50</td>
<td>21.9</td>
<td>715</td>
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</tbody>
</table>

MCV, motor conduction velocity; CMAP, compound muscle action potential; SCV, sensory conduction velocity; SNAP, sensory nerve action potential; CK, creatine kinase; ND, not done. Abnormal values are expressed in bold letters. Values in parentheses are normal values.
He had walking difficulty since 40 years of age, had become bedridden, and died of respiratory disease at the age of 50.
It is interesting to note that Brazil has held huge immigrants from Japan since 1908, reaching eighteen million at present. In addition, more than one third of the initial Brazilian immigration came from Okinawa islands. The people from Okinawa prefecture have immigrated to American continents, including Brazil (approximately 130,000), United States (80,000), Peru (40,000), Argentina (30,000), Bolivia (10,000), Canada (1,500), and Mexico (650), and other countries (7,250). We can thus assume that HMSN-P is not only limited in Japan, but might have spread worldwide, especially in the countries which holds with many Okinawan immigrants.
It is speculated that there are patients diagnosed as having “Familial ALS or SMA” in the world including South and North America.
The HMSN–P gene is mapped to Chromosome 3, specifically to 3p11.2–3q13.1. The gene is indicated by a diagram with markers including D3S1563, D3S3654, D3S3652, D3S3632, D3S1591, D3S1291, D3S1281, D3S3638, D3S3652, D3S3632, D3S1591, and D3S1291. The map distance is marked in cM, with specific distances indicated by 0.8, 1.3, 0.1, 2.8, 0.1, and 0.0.

References:

HMSNP gene
Kansai type
MIM*604484
HMSNP gene
Okinawa type
(Shiga)
Whole genome analysis for HMSN-P gene locus using SNP array
High lod score at centromere region of ch. 3

Several SNPs with LOD>5 are located in 43.8 Mb region at Ch.3.
Construction of BAC clone contig derived from HMSN–P patients

Two Mb candidate region at 3q12-13

BAC clones

Full sequencing using the next generation autosequencer

Collaboration with Dr. Kaname in Ryukyu University
Analysis of HMSN-P gene by the next generation autosequencer

One billion base sequence in 75hrs
Scope of this research

The gene locus has been mapped on the chromosome 3; however, the causative gene has yet to be identified. Genetic analyses of HMSN-P pedigrees living in Brazil and other countries will definitely accelerate the gene cloning because entry of other ethnic chromosomes and genetic crossover are expected in heterogeneous populations. In addition to the genetic study, molecular biological and pathological studies including oxidative stress in nervous system are important to clarify the pathomechanism of HMSN-P using human materials obtained from Japan and other countries.

The purpose of this research is to clarify the global epidemiology, pathomechanism and therapeutic strategy for HMSN-P in collaboration with south American neurologists and neuropathologists, especially with Prof. Marchiori, Dr. Teresa and Dr. Angelina Lino in Sao Paulo University.
Tasks of this overseas scientific research are:

- To clarify the epidemiology of HMSN-P in Brazil and other countries in South America, especially the countries with numerous immigrants from Okinawa, and compare the clinical, electrophysiological and neuropathological findings of patients with HMSN-P in Japan and those in south American countries.
- To conduct seminars to develop the knowledge for HMSN-P in south American neurologists and neuropathologists.
- To clarify the pathological findings of HMSN-P in Brazil and other countries.
- To identify the responsible gene for HMSN-P using DNA obtained from south American and Japanese patients by the next generation sequencer.
- To develop an animal model for HMSN-P after the gene is identified, and develop the therapeutic strategy.
Significance and expected results of this research

Our research team has been so far unique in studying this disease. This research collaboration with Brazilian neurologists will result in expansion of significant information to clarify the molecular and pathological basis of HMSN-P and eventually to develop a possible therapeutic approach. Because the disease develops usually in the fourth decade of life, mutant genes have a higher chance to be transmitted to the next generation. It is urgently needed to clarify the disease mechanism as early as possible.

The electrophysiological and neuropathological studies have suggested that HMSN-P is essentially a neuronopathy in which motor and sensory neurons in anterior horn or dorsal root ganglions, respectively, are induced to cell death. To clarify the pathomechanism of HMSN-P may contribute to the clarification of other neurological diseases, such as ALS and SMA.

Lastly this unique collaboration study will definitely contribute to the centennial partnership between Japanese and Brazilian neurologists.
## Different subtypes of FALS and their genetic determinants

<table>
<thead>
<tr>
<th>ALS type</th>
<th>Onset</th>
<th>Inheritance</th>
<th>Locus</th>
<th>Gene</th>
<th>Protein</th>
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Archives Italiennes de Biologie, 149: 65–82, 2011.
Are the clinico-pathologic features of HMSN-P rather similar to those of MND with sensory neuropathy?

Journal of Neurology, Neurosurgery & Psychiatry (in press)

Brainstem and spinal cord motor neuron involvement with optineurin inclusions in proximal–dominant hereditary motor and sensory neuropathy.

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Commentary to the paper M. Nakagawa (in preparation)

A new classification of proximal-dominant hereditary motor and sensory neuropathy (HMSN-P) as familial motor neuron disease with sensory neuronopathy.
(B, C) The hypoglossal nucleus shows mild neuron loss (B) compared to the control (C).
(D) Severe myelin pallor of the posterior and lateral columns and atrophy of the anterior horn of the cervical cord.
(E) Severe neuronal loss, atrophy of the remaining neurons (arrows), and gliosis in the anterior horn of the cervical cord. (F) Neuronal loss and gliosis of Clarke’s nucleus of the thoracic cord.
(G) Mild neuronal loss of Betz cell (arrow ahead) and cluster of macrophages (arrow) in the precentral gyrus.
(H) Severe neurogenic atrophy of iliopsoas muscles against a background of fatty tissue.
(I) Both large and small myelinated fibers are markedly decreased without onion-bulb formation in the sural nerve.
(J) Ubiquitin-positive inclusions of motor neurons in the facial nucleus.
(K) OPTN-positive inclusion of motor neurons in the hypoglossal nucleus.

(L–N) Double-immunofluorescence staining for ubiquitin (L, red) and OPTN (M, green) in residual neurons in the abducens nucleus shows that ubiquitin inclusions are largely co-localized with OPTN inclusions (N)
A number of issues remain to be elucidated in HMSN-P, and among others, the questions include: How is the motor pathology related to the sensory counterpart? What is the causative gene for the disease? How are large HMSN-P families in Okinawa and Kansai related? The global epidemiology, pathomechanism and therapeutic strategy for HMSN-P remained so far. Because the disease develops usually in the fourth decade of life, mutant genes have a higher chance to be transmitted to the next generation, underscoring the urgency of seeking the pathomechanism.

The quest for the search of the exact pathomechanism of HMSN-P may contribute to the clarification of other neurological diseases, such as FALS and SMA.
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