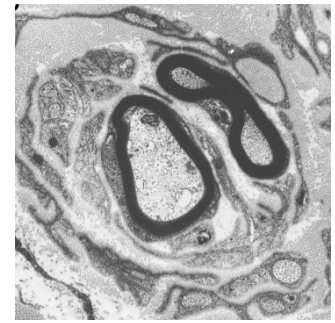
Hereditary neuropathy

CMT and HMSN-P

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

Masanori Nakagawa, M.D.

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)


Milwaukee
Seattle
関西空港
Atlanta
7月31日～8月7日
Sao Paulo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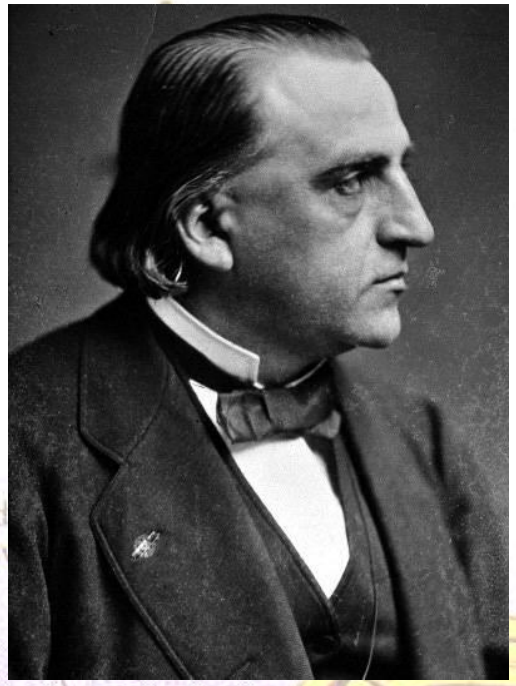
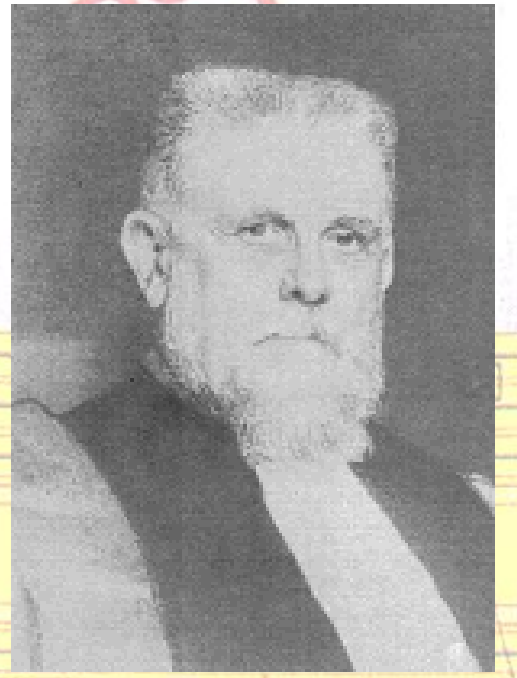
HC

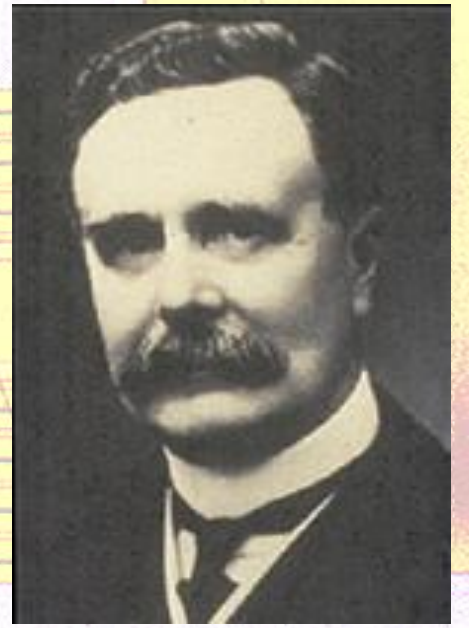
Charcot-Marie-Tooth disease (CMT) is the most commonly inherited peripheral neuropathy and is found worldwide among all races and ethnic groups. Discovered in 1886 by three physicians, Jean-Martin Charcot, Pierre Marie, and Howard Henry Tooth, CMT affects an estimated 2.6 million people.



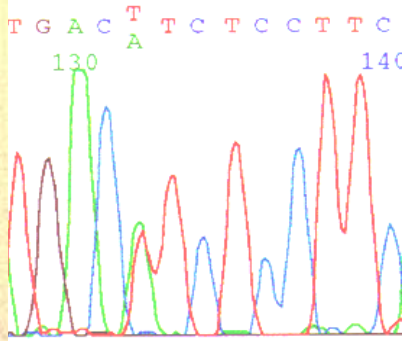
Charcot , Jean-Martin
1825-1893

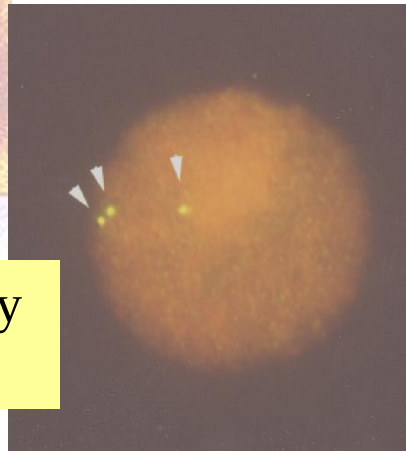


Marie , Pierre
1853-1940

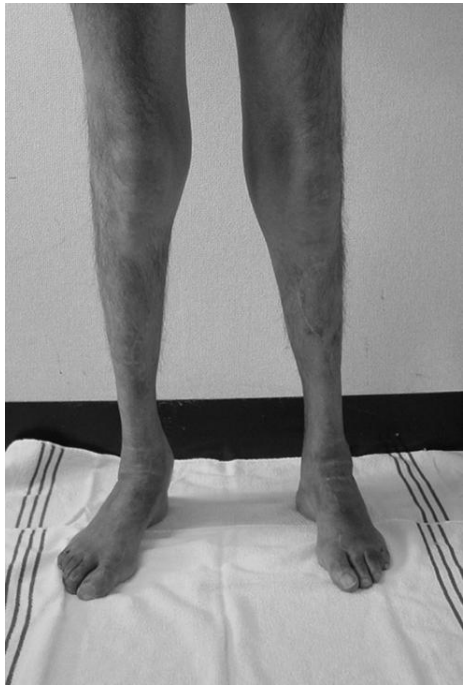


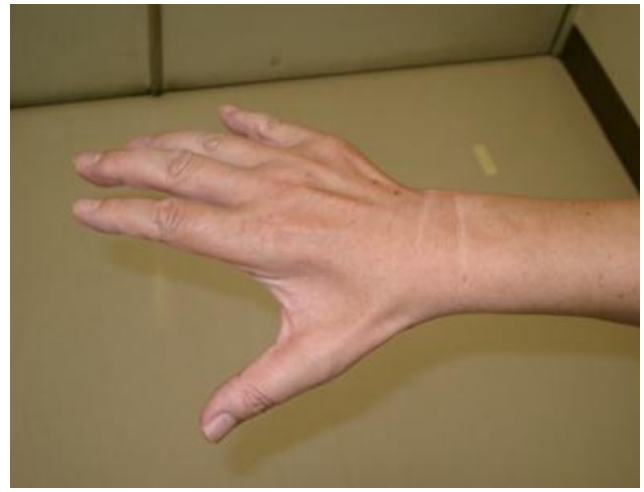
Tooth, Howard Henry
1856-1925

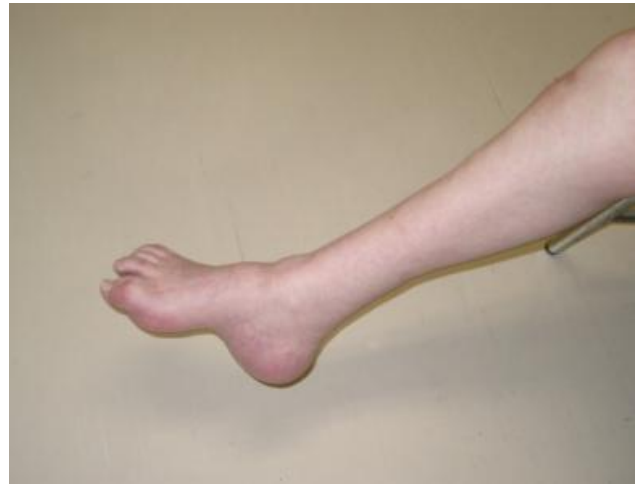


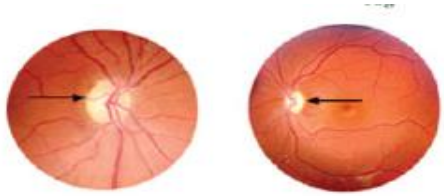


Clinical presentation of CMT









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.

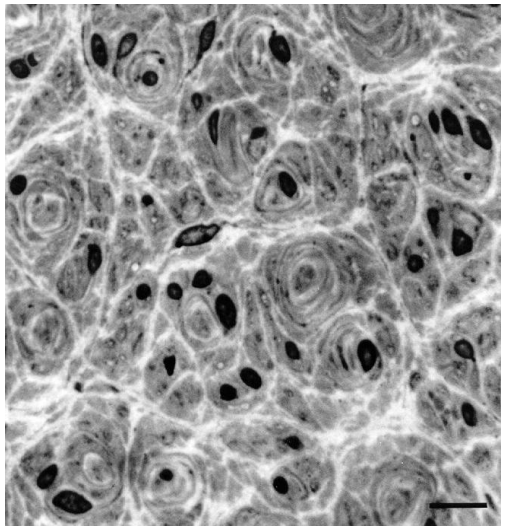
The uncommon associated features such as involvement of cranial nerves, vocal cord palsy, pupillary abnormalities, glaucoma, optic atrophy, pyramidal involvement, predominant upper-limb involvement, prominent sensory abnormalities, and proximal dominant involvement.

CMT1　CMT (Intermediate forms)　CMT2

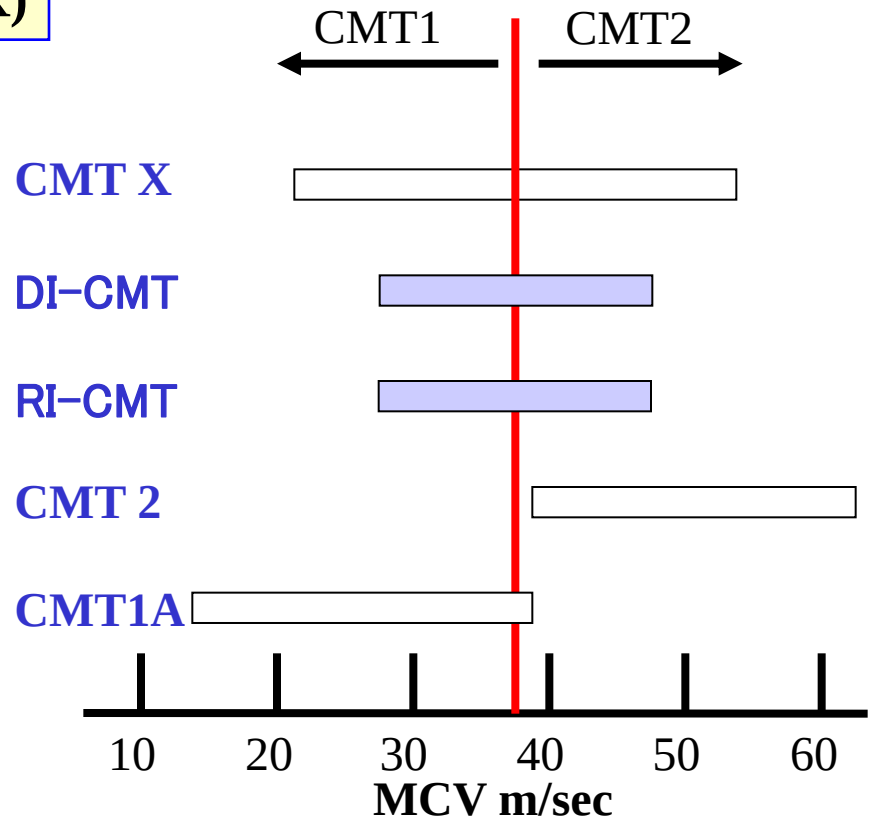
NCV in median nerve

38m/sec

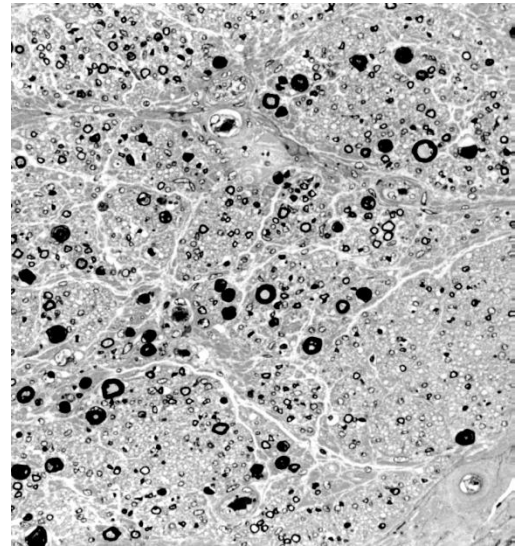
Demyelinationg CMT
CMT1(AD), CMT4(AR)



CMAP：almost normal
or slightly delayed
Segemental demyelination
Onion bulb formation



Axonal CMT
CMT2（AD, AR)

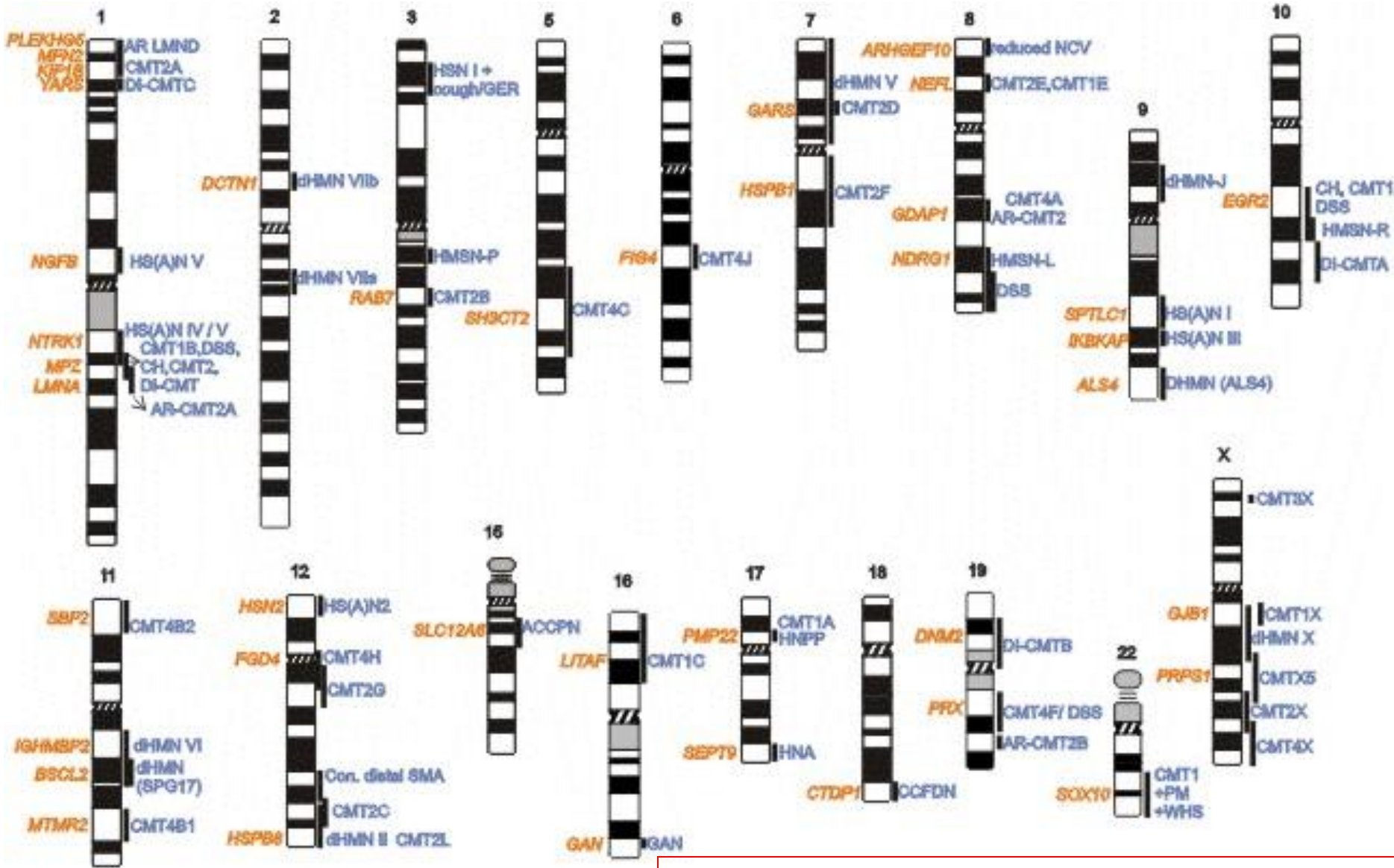


CMAP：markedly reduced
Decreased myelinated fiber density

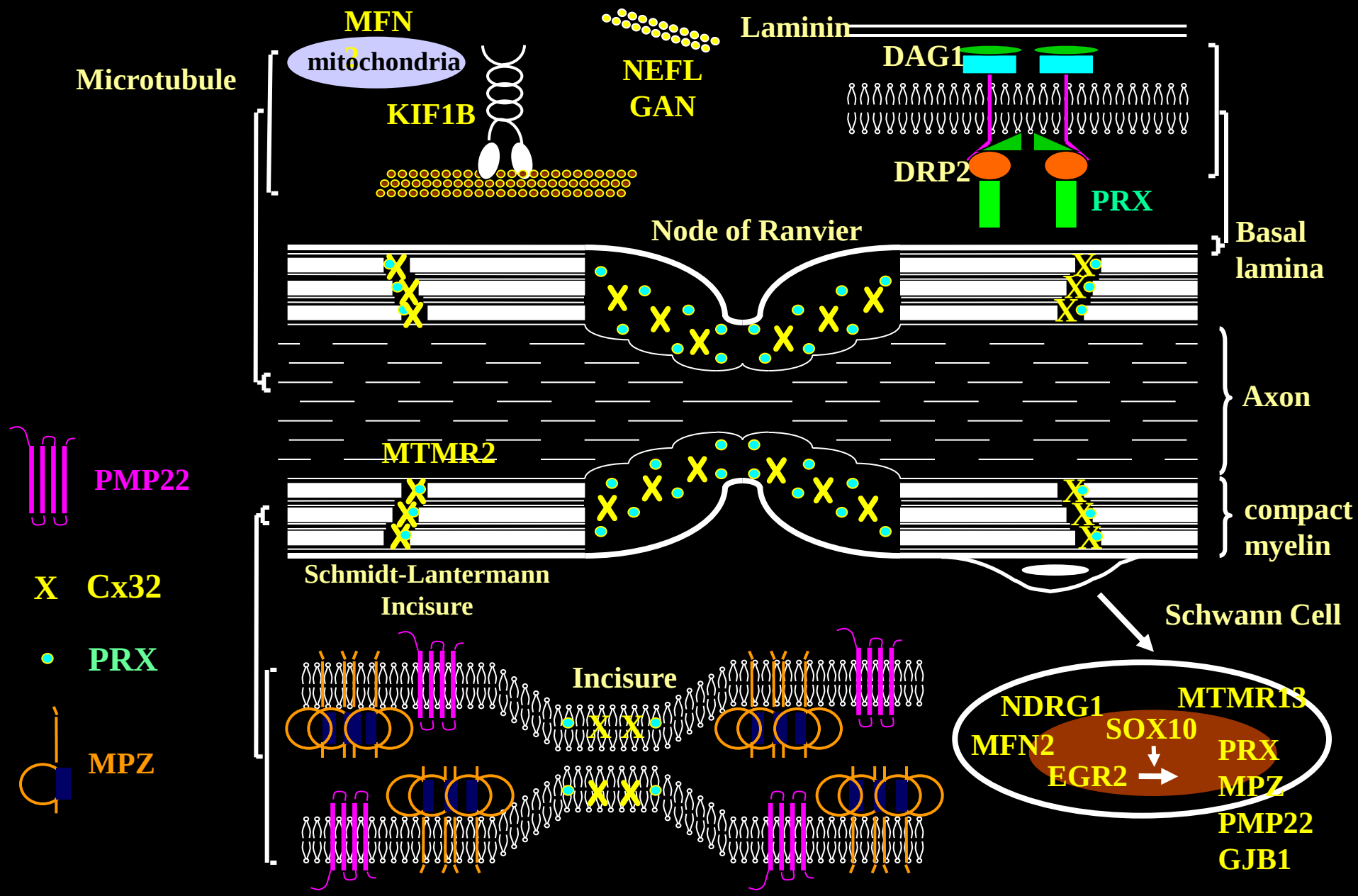
Intermediate CMT : unable to classify by **38m/sce, DI-CMT、RI-CMT**

Genes and loci of Inherited Peripheral Neuropathies

About 50 loci and 40 genes have been identified



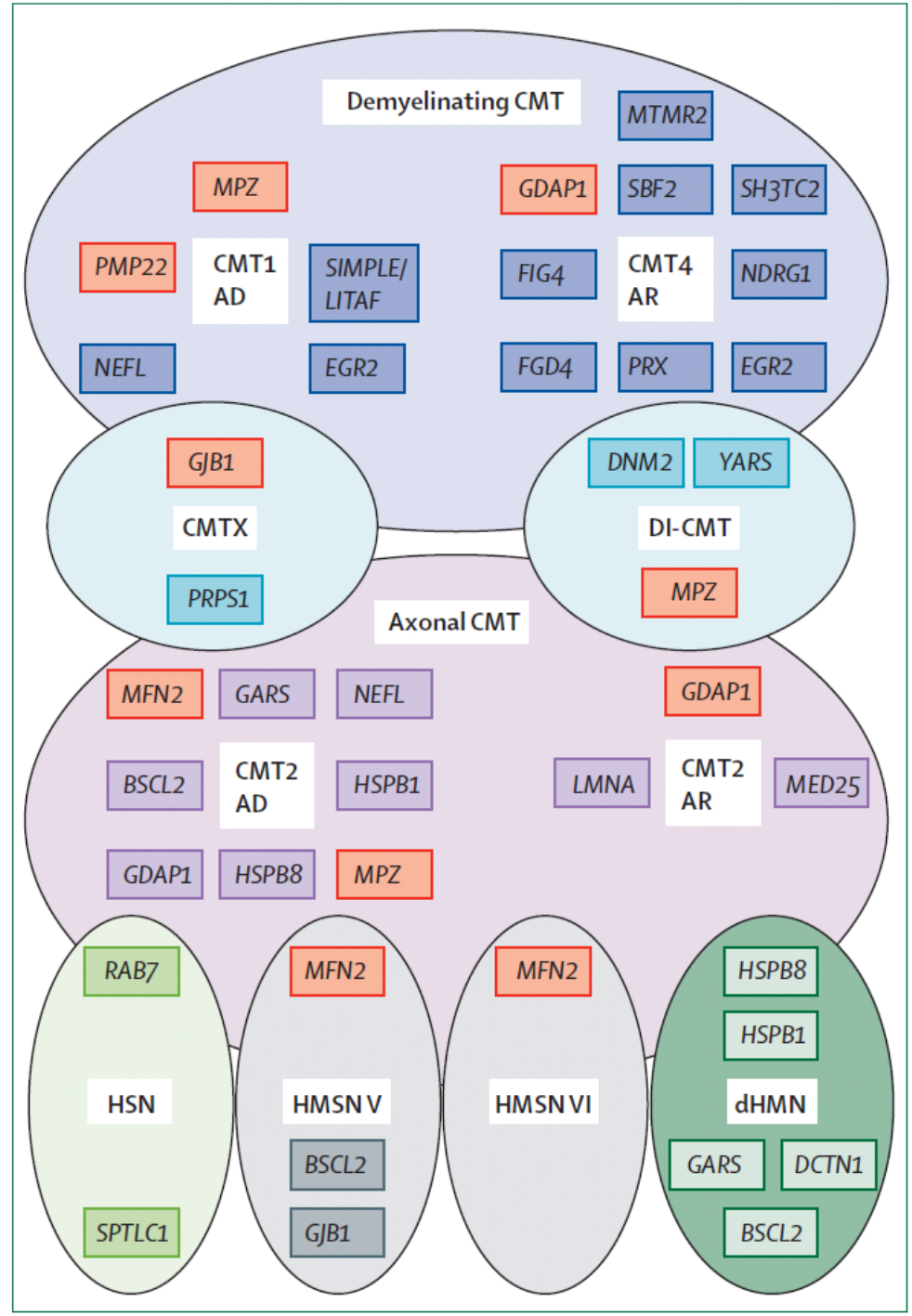
http://www.molgen.ua.ac.be/CMTMutations/Home/IPN.cfm



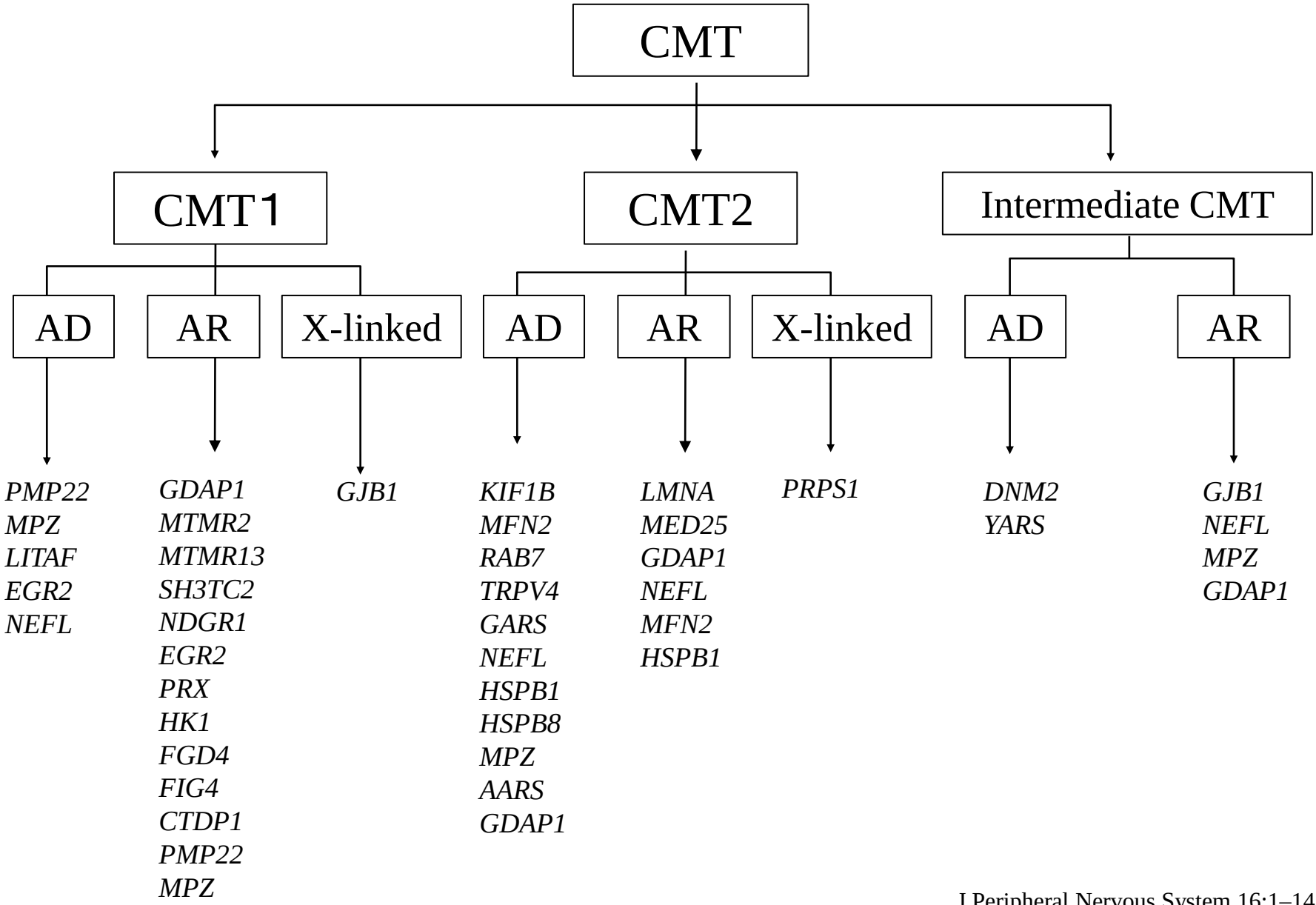
Saifi GM, et al. J Investigative Med 51:5:261-283, 2003

Different forms of CMT disease and associated genes

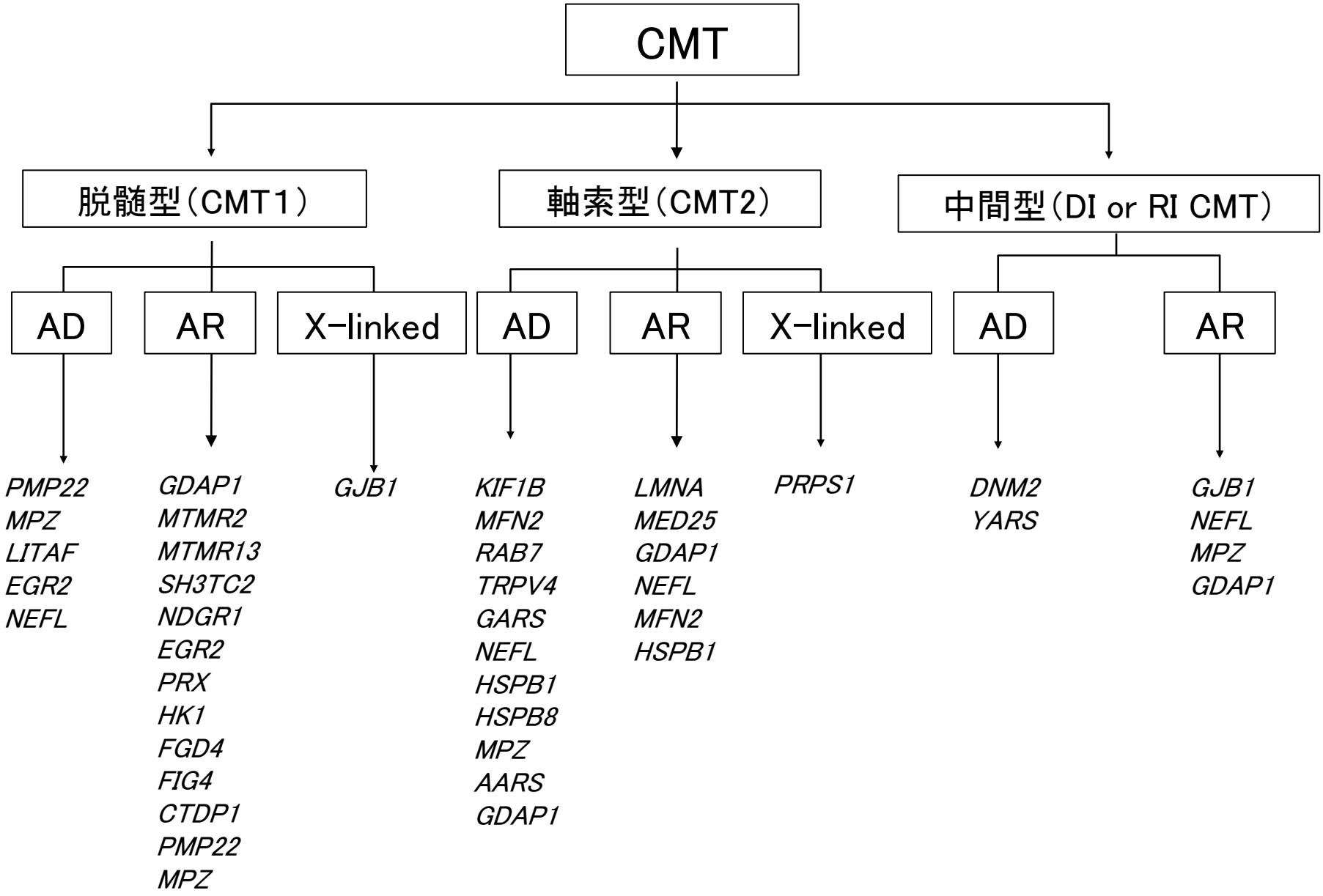
Lancet Neurol 2009; 8: 654–67



Genetic classification of CMT



J Peripheral Nervous System 16:1–14 (2011)


CMT
脱髄型（CMT1）
軸索型（CMT2）
中間型（DI or RI CMT）
AD
AR
X-linked
AD
AR
X-linked
AD
AR
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
LMNA
MED25
GDAP1
NEFL
MFN2
HSPB1
PRPS1
DNM2
YARS
GJB1
NEFL
MPZ
GDAP1

Incidence of CMT related genes in USA, Italy and Japan

Abe A, Hayasaka K, et al. J human Genet (in press)n

Gene mutations in demyelinating CMT

	PMP22 dupli-cation	*PMP22*	*MPZ*	*LITAF*	*NEFL*	*GJB1*	*GDAP1*	*MTMR2*	*MTMR13*	*EGR2*	*PRX*	*DNM2*	*YARS*	Unknown	Total
Japan	53 23.3%	10 4.4%	20 8.8%	0 0%	8 3.5%	19 8.5%	0 0%	0 0%	0 0%	1 0.4%	5 2.2%	0 0%	0 0%	111 48.9%	227
Italy	98 57.6%	2 1.2%	4 2.3%	N.D.	N.D.	12 7.1%	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	54 31.8%	170
USA	79 54.1%	5 3.4%	5 3.4%	N.D.	N.D.	8 0 5.5%	0 0%	N.D.	N.D.	1 0.7%	1 0.7%	N.D.	N.D.	51 34.9%	146

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

Abe A, Hayasaka K, et al. J human Genet (in press)

Gene mutations in axonal CMT

	MFN2	*RAB7*	*GARS*	*NEFL*	*HSP27*	*MPZ*	*HSP22*	*GDAP1*	*GJB1*	*DNM2*	*YARS*	Unknown	Total
Japan	14 11.0%	0	1 0.8%	0	0	5 4.0%	0	1 0.8%	6 4.7%	0	0	100 78.7%	127
USA (2011)	21 21.9%	–	3 3.1%	4 4.2%	–	–	–	5 5.2%	–	–	–	63 65.6%	96

Commentary

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

Masanori Nakagawa

Journal of Human Genetics (2011) **0**, 000–000. doi:10.1038/jhg.2011.32

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.*

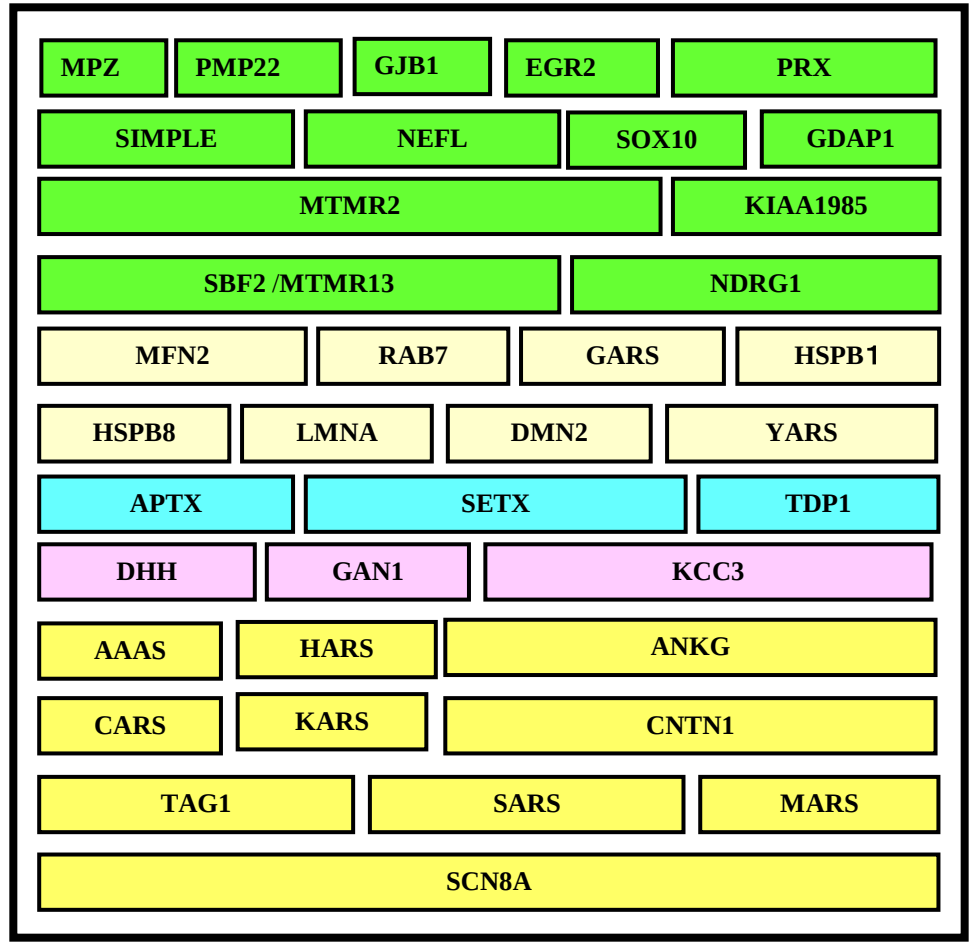
DNA chip for hereditary neuropathy diagnosis

Known genes: 28 genes

Candidate genes: 11 genes

DNA Chip（resequencing chip）
110.938 bp on the chip

Gene Chip image（100K array)

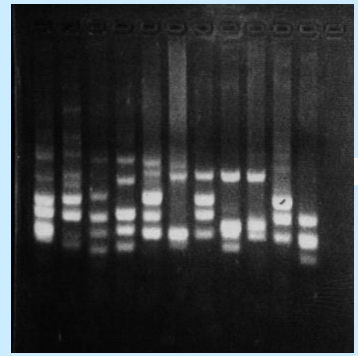


It is able to screen 28 genes and 11 candidate genes at once.

Genetic diagnosis system for hereditary neuropathy diagnosis
High throughput and low cost protocol

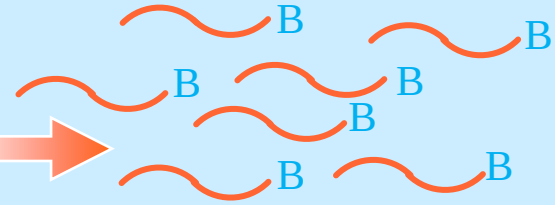
Multiplex PCR reaction

Pts DNA sample
no PMP22 duplication
CMT2



PCR products
Pooled PCR (Max 548 reactions)

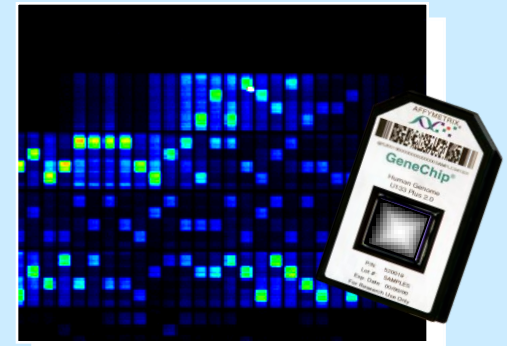
DNase I digestion



End-labeled fragments

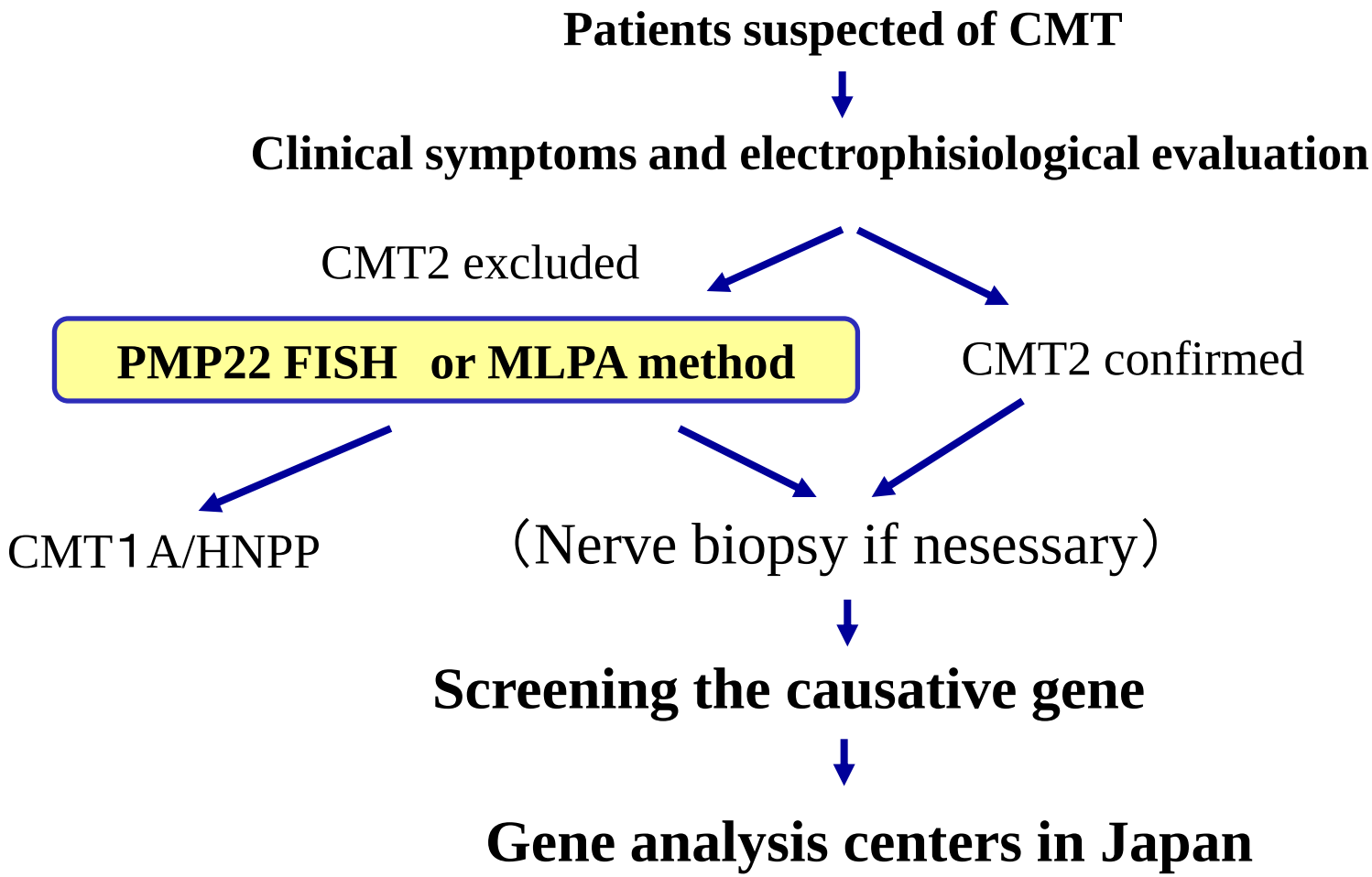
DNA chip for hereditary neuropathy diagnosis

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



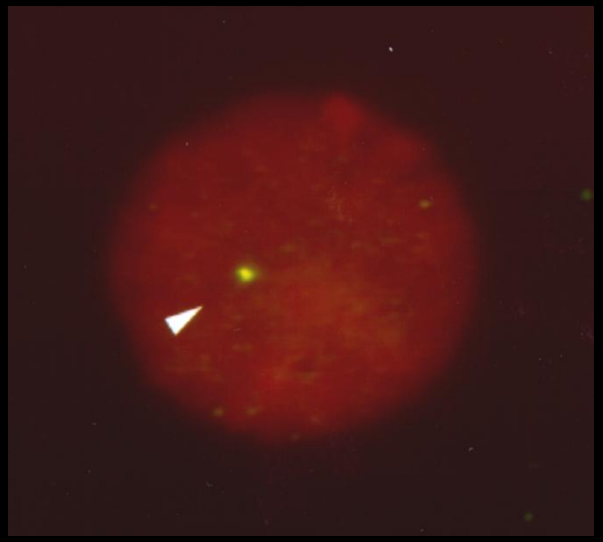
Microarray analysis
Gene Chip Scanner 3000

Diagnostic system for CMT



PMP22 deletion/duplication detected by FISH

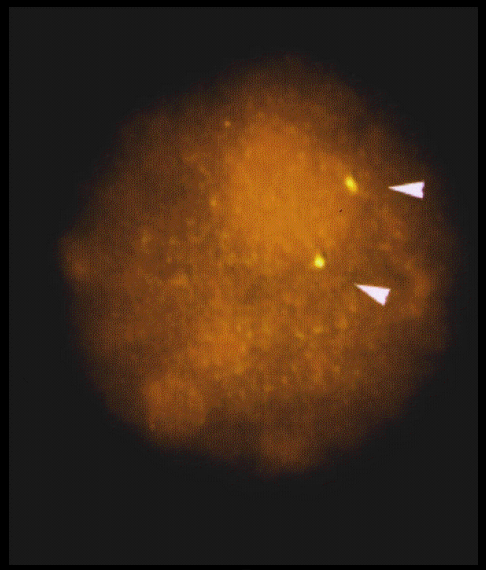
One copy of *PMP22*



HNPP

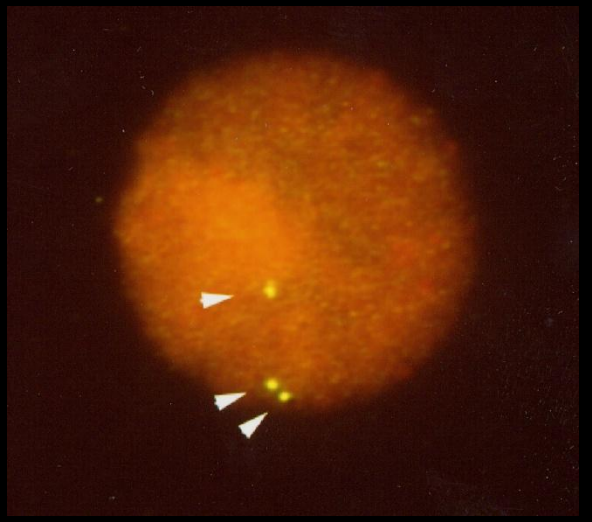
（Hereditary Neuropathy with liability to pressure palsies）

Two copies of *PMP22*



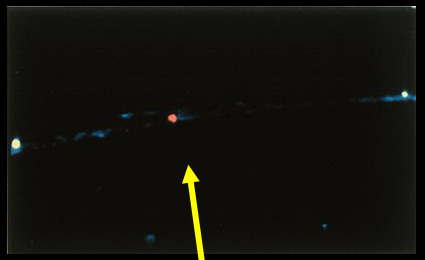
Normal

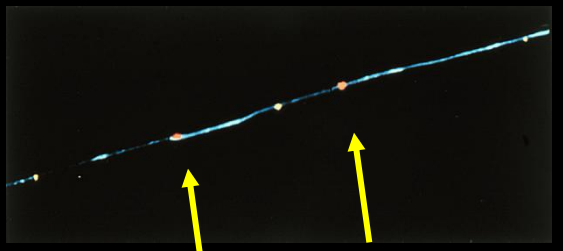
Three copies of *PMP22*



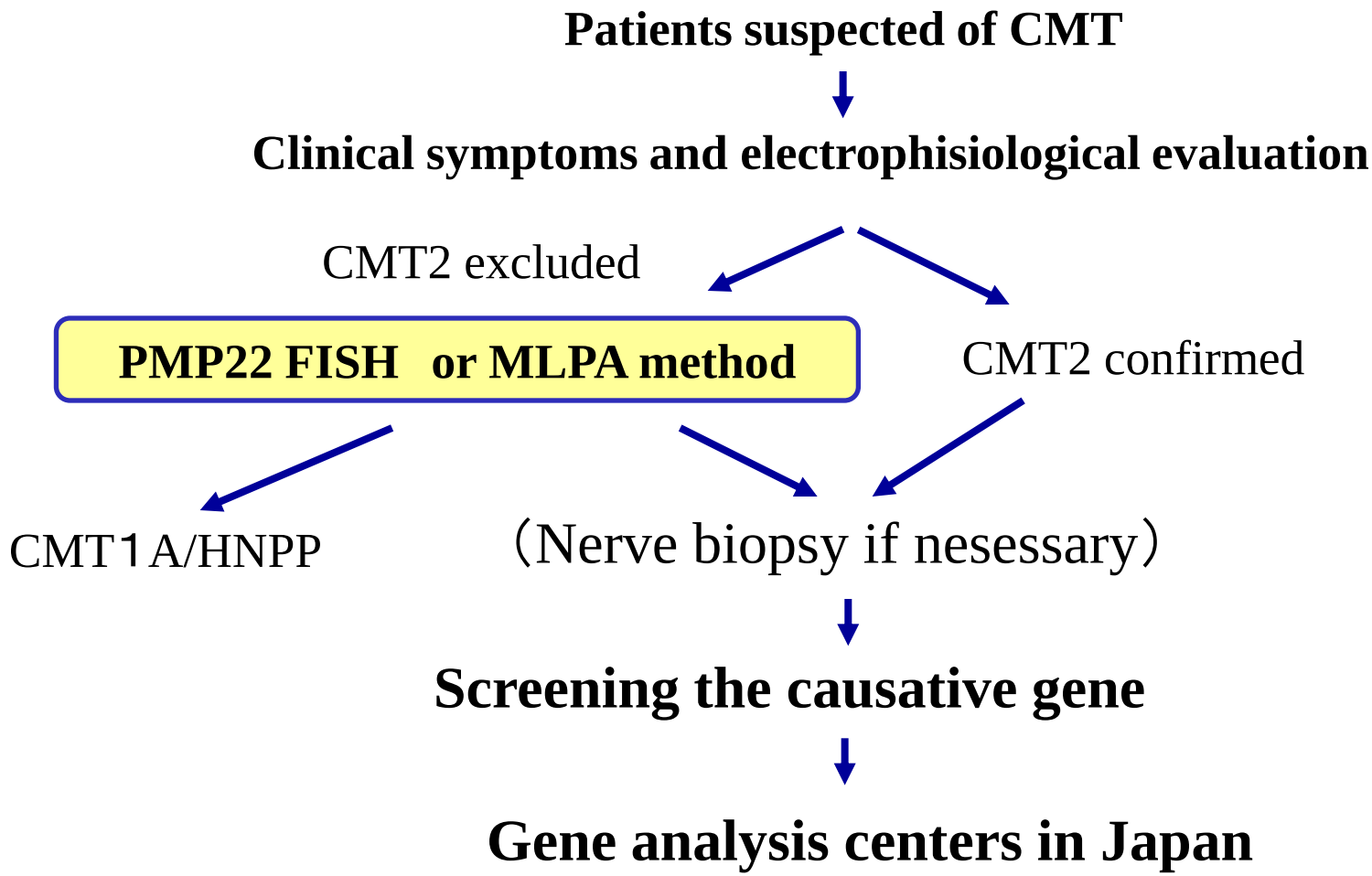
CMT1A

Fiber FISH





Diagnostic system for CMT



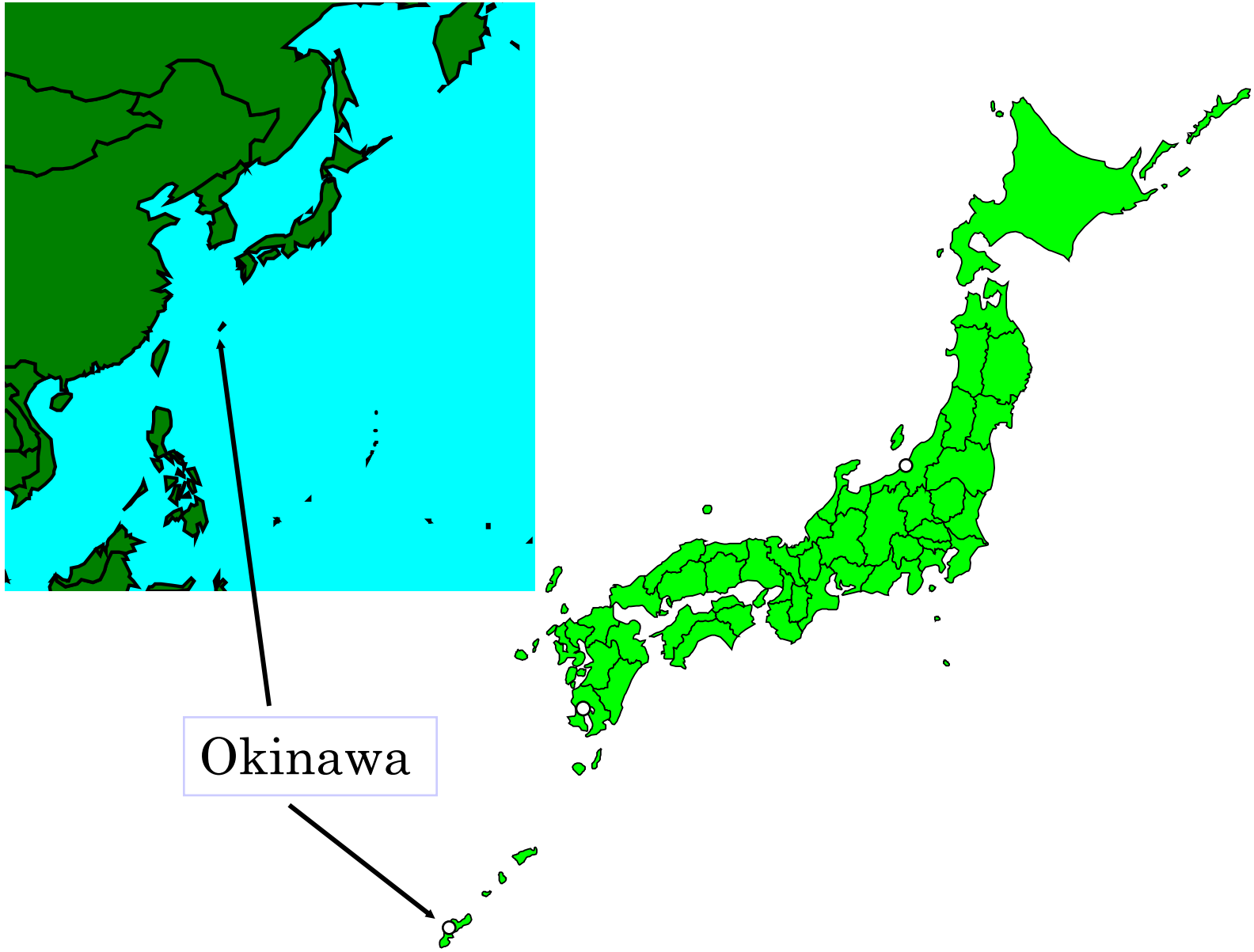
Kagoshima University, Prof. Takashima is organizing

cmtdiag@m3.kufm.kagoshima-u.ac.jp

Autosomal dominant hereditary motor and sensory neuropathy with proximal dominancy (HMSN-P)

Scientific background of this research -1-

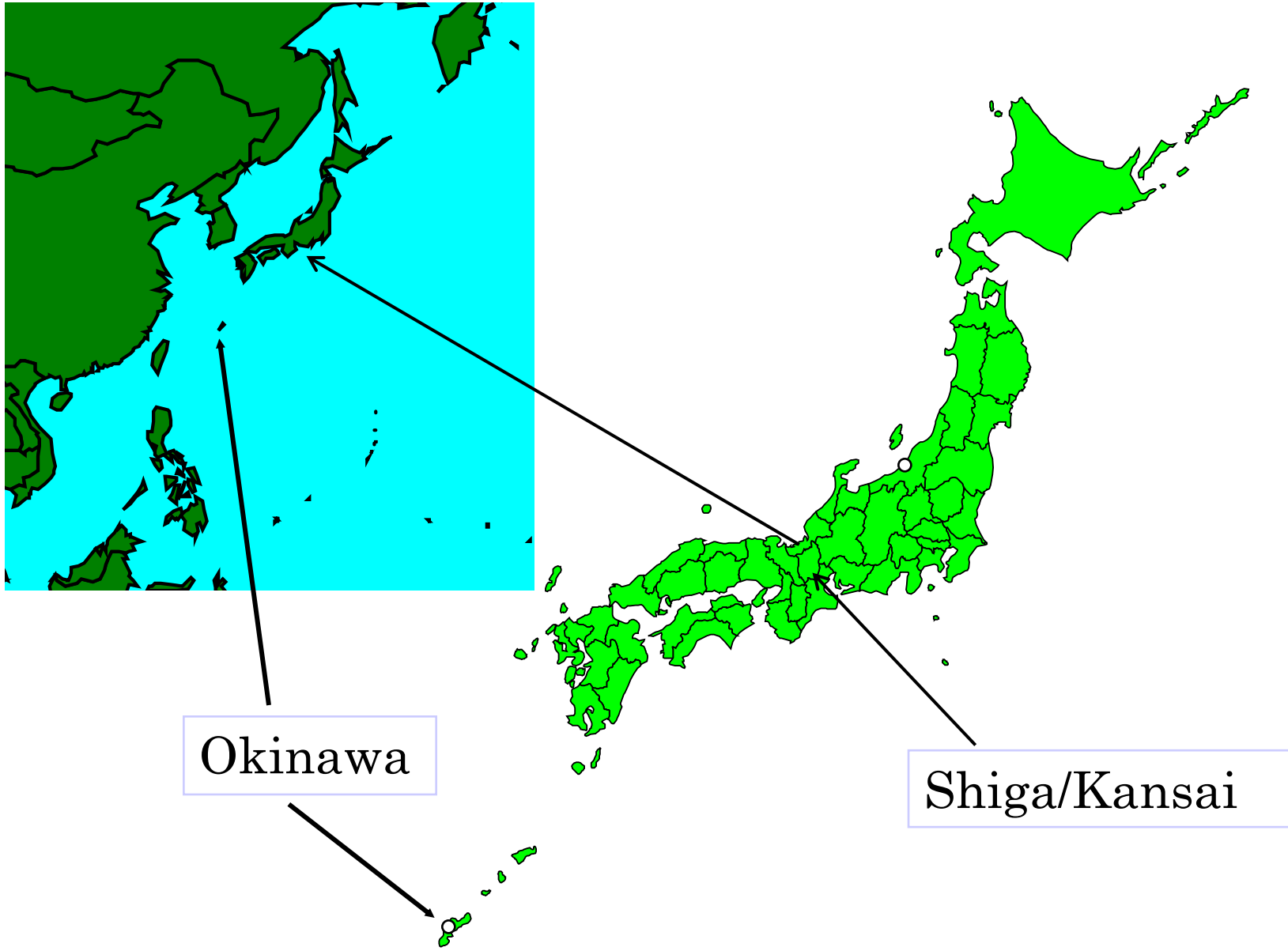
HMSN-P is an autosomal dominant slowly progressive neuromuscular disease that we first described in patients from Okinawa, a southern archipelago in Japan. The clinical features of HMSN-P include proximal dominant neurogenic atrophy with fasciculations, painful muscle cramp, sensory involvement, and 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

Scientific background of this research -2-

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.

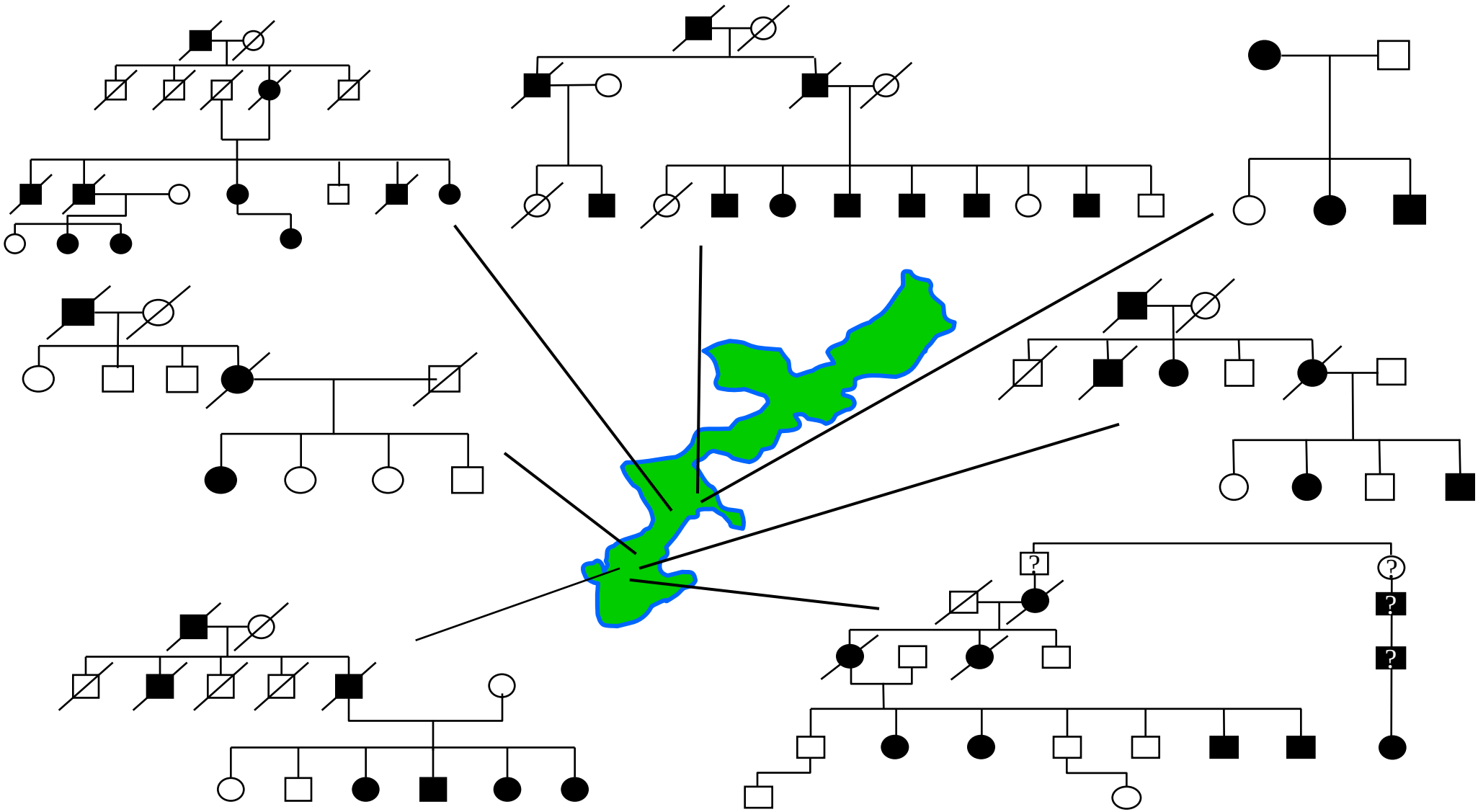
The gene locus of HMSN-P has been mapped to an overlapping centromeric region on chromosome 3 in two independent linkage analyses, one from Okinawa family and another family reported in Shiga prefecture in mainland Honshu, Japan.


Okinawa
Shiga/Kansai

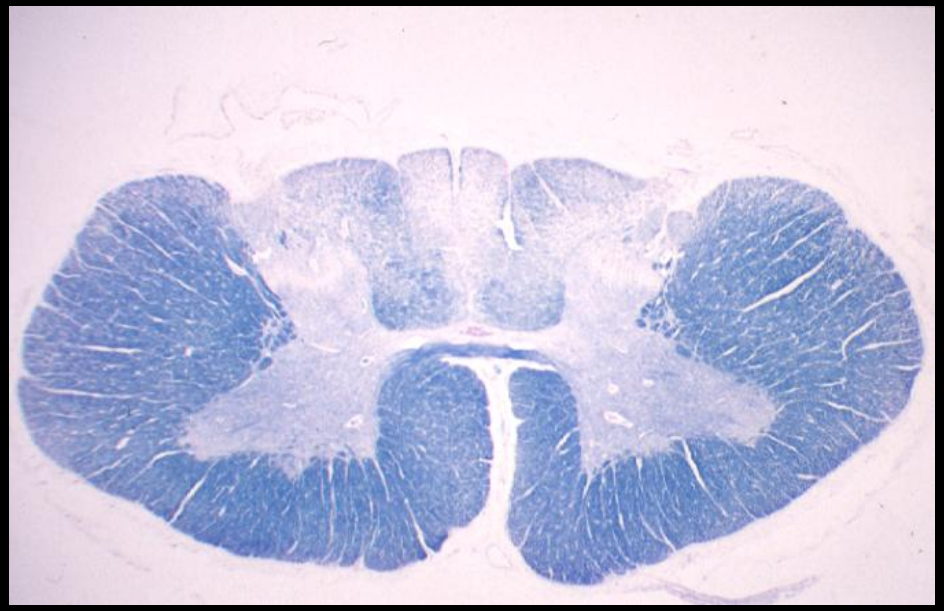
Clinical and pathological features in HMSN-P

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.

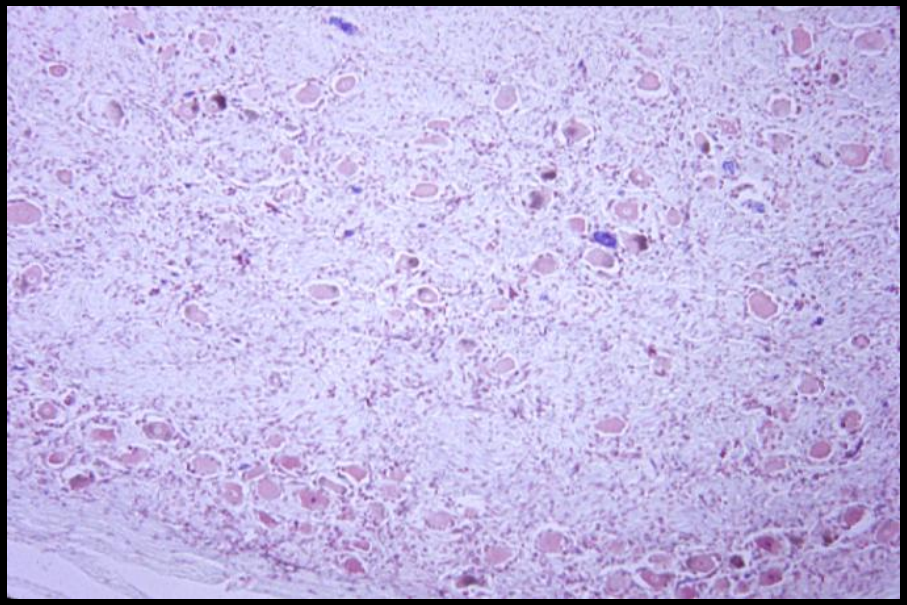
More than 100 patients with HMSN-P, 8/10^5 population,
are estimated in Okinawa by our epidemiological study.
Only 7 of 18 families with HMSN-P are shown in this figure.



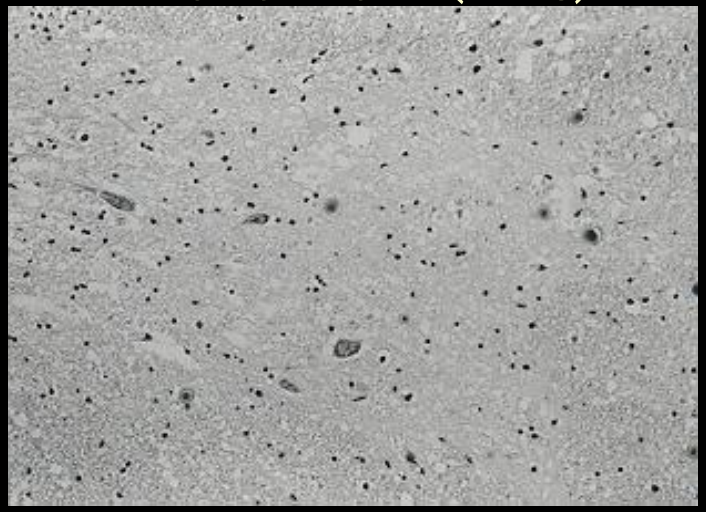
Transverse section of spinal cord (C8)



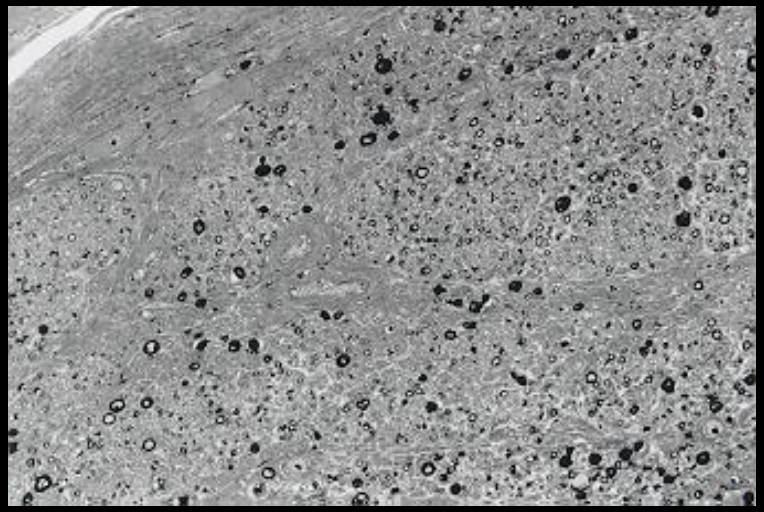
Dorsal root ganglion (L5)



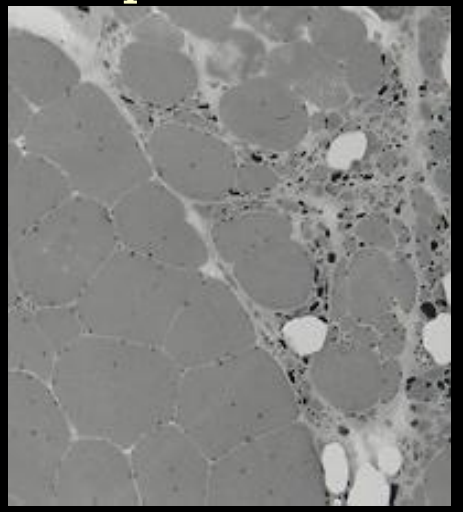
Anterior horn (Th 8)



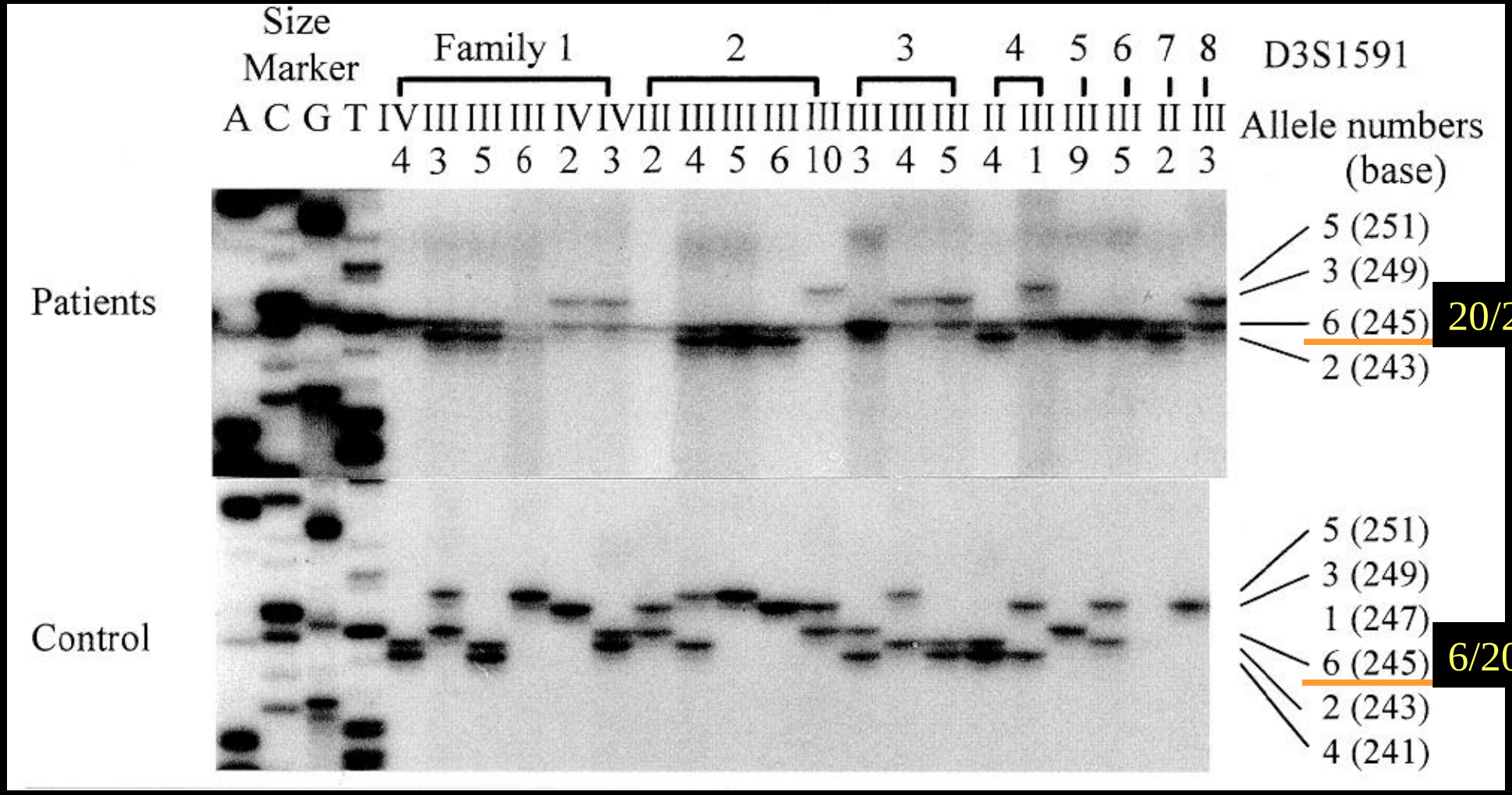
Tibial nerve



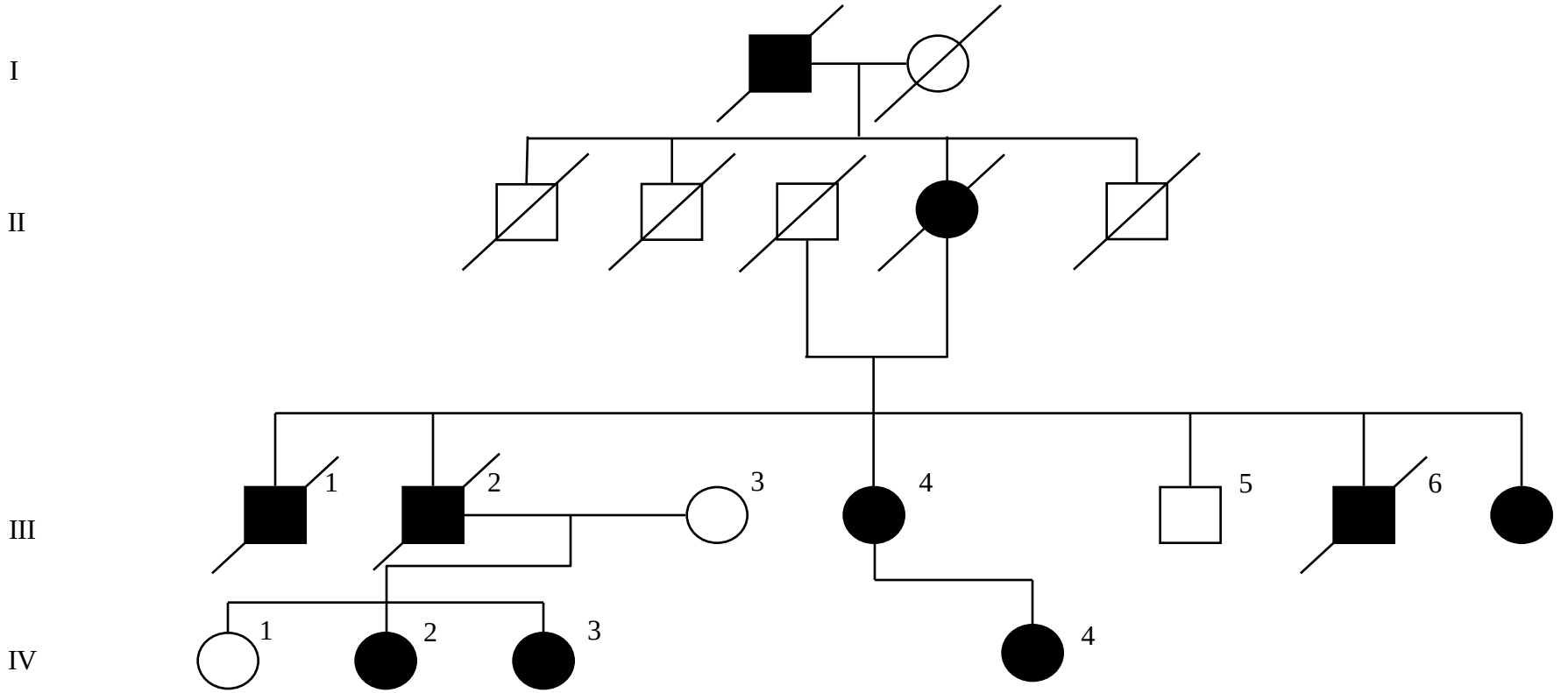
Biceps brachii muscle



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



Family 1



D3S3652	151	151	**159**	153	**159**	153	151	153	**159**	151	**159**	155	151	151	**159**	153	**159**	151
D3S3632	142	144	**140**	140	**140**	140	142	140	**140**	142	**140**	140	142	144	**140**	140	**140**	142
D3S1591	250	240	**242**	246	**242**	246	250	246	**242**	240	**242**	242	238	240	**242**	238	**242**	240
D3S1291	184	188	**188**	186	**188**	186	184	186	**188**	188	**188**	186	188	188	**188**	188	**188**	188
A281WA5	252	242	**252**	252	**252**	252	252	252	**252**	252	**252**	252	252	252	**252**	244	**252**	252
D3S1563	223	223	**223**	223	**223**	223	223	223	**223**	223	**223**	223	223	223	**223**	215	**223**	223
D3S3654	160	158	**160**	160	**160**	160	160	160	**160**	158	**160**	160	160	158	**160**	162	**160**	158
D3S1281	129	115	**119**	119	**119**	119	129	119	**119**	115	**119**	137	137	115	**119**	115	**119**	115
D3S3638	160	152	**152**	160	**152**	160	160	160	**152**	152	**152**	164	156	152	**152**	164	**152**	152

A New Type of Hereditary Motor and Sensory Neuropathy Linked to Chromosome 3

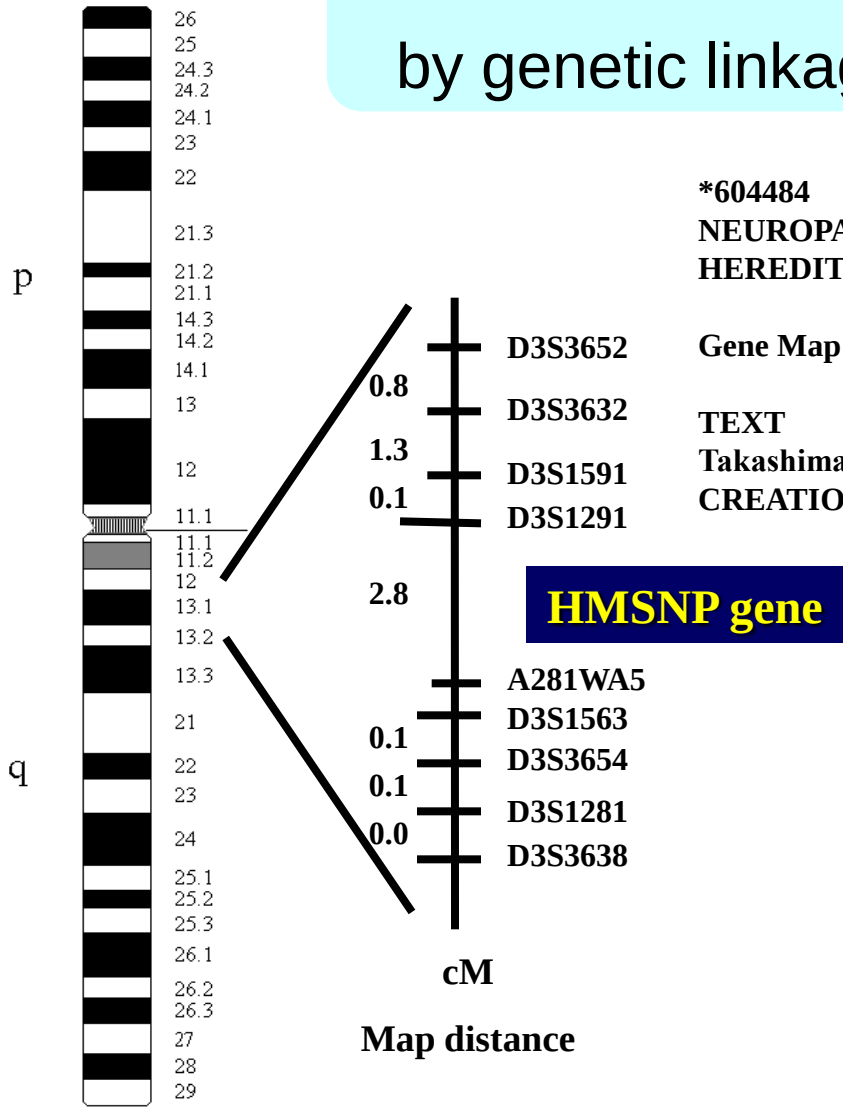
Hiroshi Takashima, MD,*† Masanori Nakagawa, MD,* Keiichi Nakahara, MD,* Masahito Suehara, MD,* Toshio Matsuzaki, MD,*† Itsuro Higuchi, MD,* Hidemasa Higa, MD,‡ Kimiyoshi Arimura, MD,* Teruo Iwamasa, MD,§ Shuji Izumo, MD,‖ and Mitsuhiro Osame, MD*

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-Alter-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.

Takashima H, Nakagawa M, Nakahara K, Suehara M, Matsuzaki T, Higuchi I, Higa H, Arimura K, Iwamasa T, Izumo S, Osame M. A new type of hereditary motor and sensory neuropathy linked to chromosome 3. Ann Neurol 1997;41:771–780

HMSN-P gene mapped to 3cM region at 3q13.1

by genetic linkage and linkage disequilibrium analysis



HMSNP gene

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

Gene Map Locus: 3q13.1

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

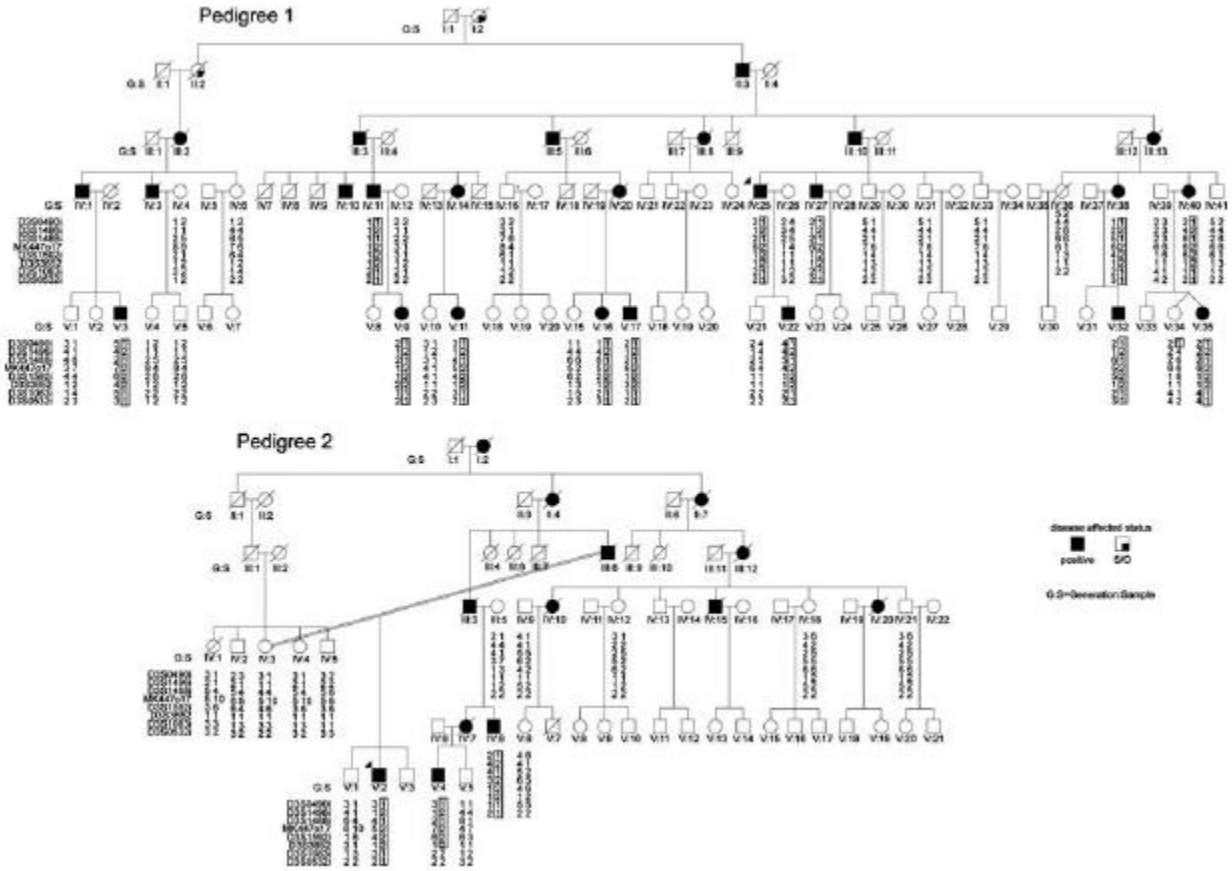
Takashima H, Nakagawa M, et al.
***Neuromuscul Disord* 9: 368-371, 1999**

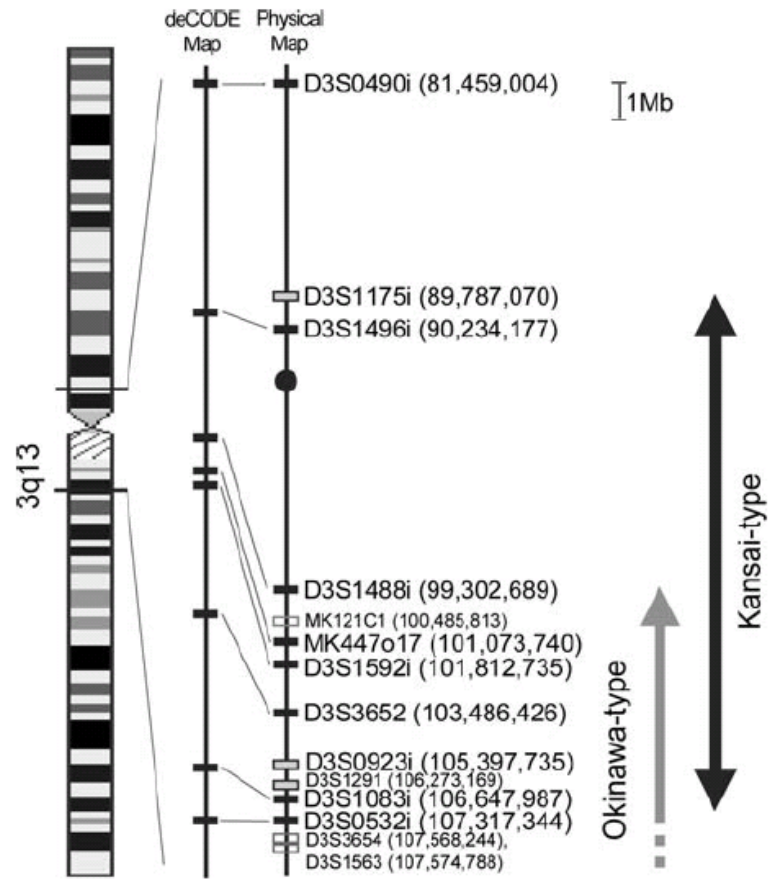
Nakagawa M, Takashima H, et al.
***Ann NY Acad Sci* 883: 449-452, 1999**

Chromosome 3

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

Maeda K, Kaji R et al. J Hum Genet 2007;52:907-14.





Comparison between Okinawa and Kansai families

	Okinawa	Kansai
Mode of inheritance	AD	AD
Onset age (year)	39.2±9.0	37.5±8.0
Unable to walk (year)	56.9±6.2	
Symptoms		
slowly progressive	+	+
proximal dominant atrophy	+	+
painful muscle cramp	+	+
fasciculations	+	+
areflexia	+	+
sensory involvement	+	+
Electrophysiological findings		
motor and sensory axonal neuropathy	+	+
Loboratory findings		
highCKnemia	+	+
hyperlipidemia, and diabetes mellitus	+	+
Pathological findings		
loss of myelinated fibers	+	+
decreased numbers of anterior horn and dorsal ganglion cells	+	+
Gene locus	**3q12-13**	**3q13.1**

Scientific background of this research -3-

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.

ELSEVIER

Clinical Neurology and Neurosurgery 109 (2007) 830–832

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www.elsevier.com/locate/clineuro

Case series

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

Kengo Maeda [a,*], Makoto Sugiura [b], Hiroko Kato [b], Mitsuru Sanada [a], Hiromichi Kawai [a], Hitoshi Yasuda [a]

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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.

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 1

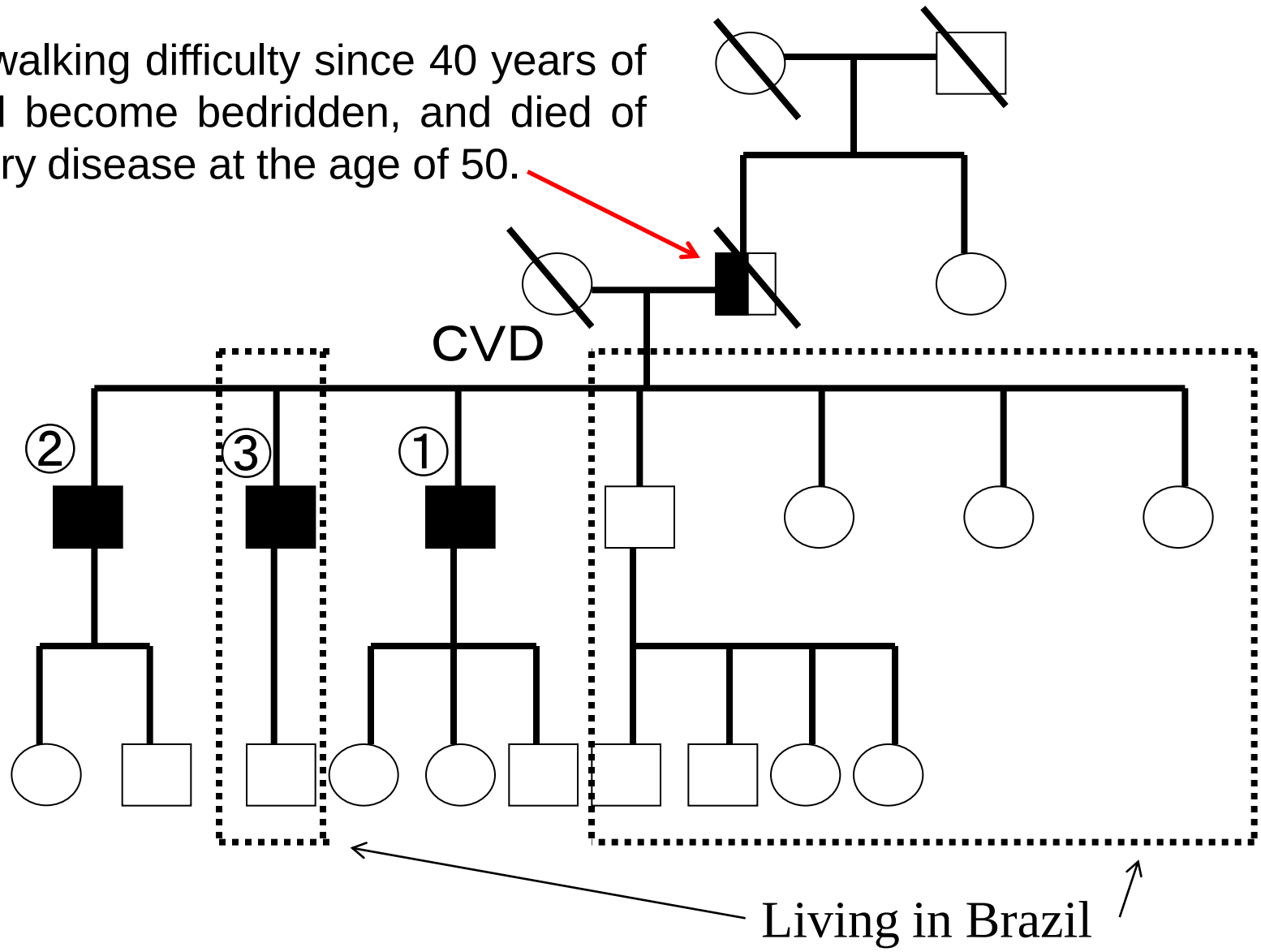
Representative data from nerve conduction studies and blood chemistry data

Case	Age at onset	Median nerve				Tibial nerve		Sural nerve		CK (51–212) (IU/l)	Cholesterol (130–220) (mg/dl)
		MCV (57.7 ± 4.9) (m/s)	CMAP (7.0 ± 3.0) (mV)	SCV (56.2 ± 5.8) (m/s)	SNAP (38.5 ± 15.6) (μV)	MCV (48.5 ± 3.6) (m/s)	CMAP (5.8 ± 1.9) (mV)	SCV (52.5 ± 5.6) (m/s)	SNAP (20.9 ± 8.0) (μV)		
1	33	57	6.6	54	**2.0**	49	13.5	57	**4.0**	**1892**	**250**
2	46	54	8.6	56	**3.2**	ND	ND	ND	ND	**552**	200
3	41	61	7.2	**36**	**2.9**	44	4.6	50	21.9	**715**	201

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.

Family tree

He had walking difficulty since 40 years of age, had become bedridden, and died of respiratory disease at the age of 50.

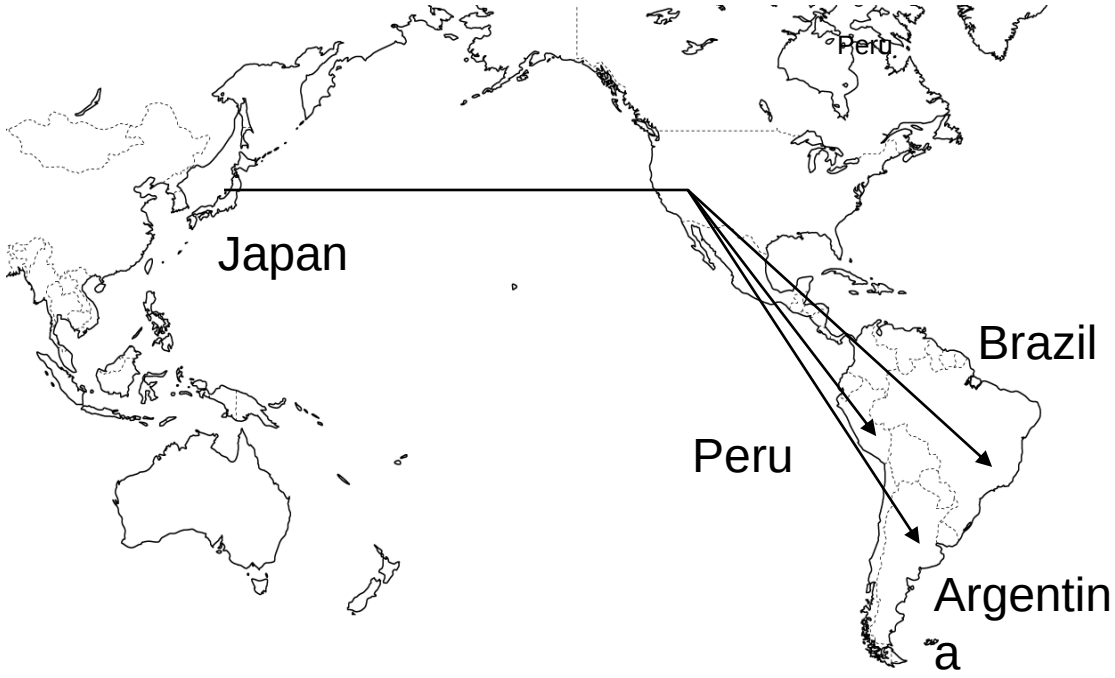


HMSN-P patients in the world?

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.

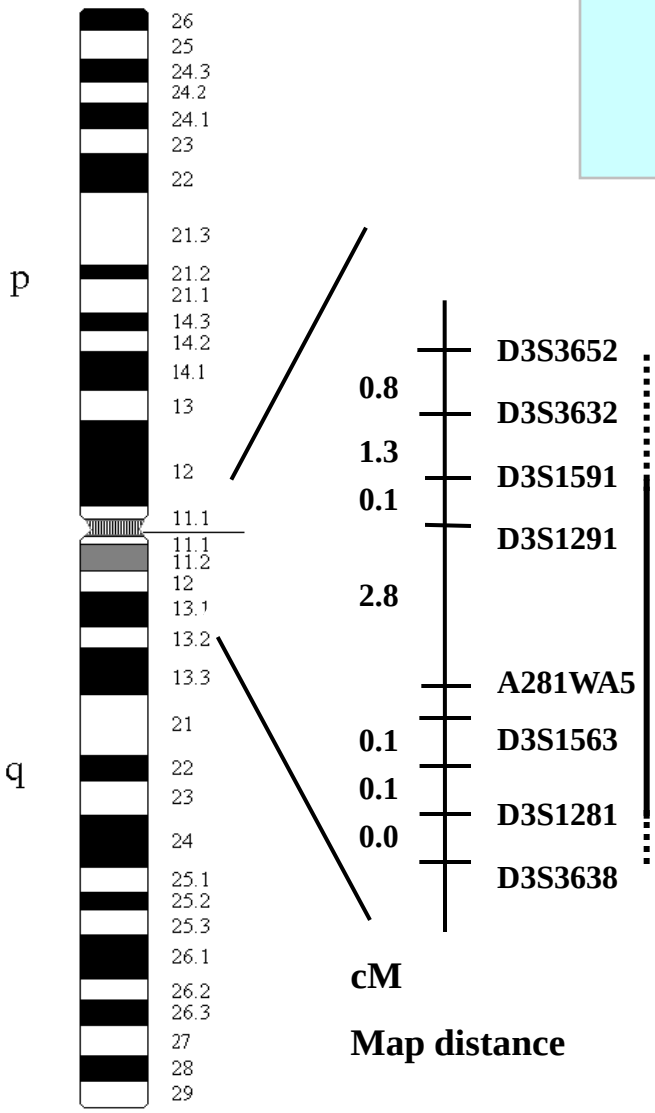
The overseas scientific research for the elucidation of the mechanism of a novel hereditary motor sensory neuropathy originated in Japan

a Grant-in-Aid for Scientific Research (B) from JSPS (21406026).
: JSPS KAKENHI (21406026)



It is speculated that there are patients diagnosed as having “Familial ALS or SMA” in the world including South and North America.

HMSN-P gene mapped to 3p11.2-3q13.1



Okinawa type

Kansai type (Shiga)

MIM*604484

HMSNP gene

Chromosome 3

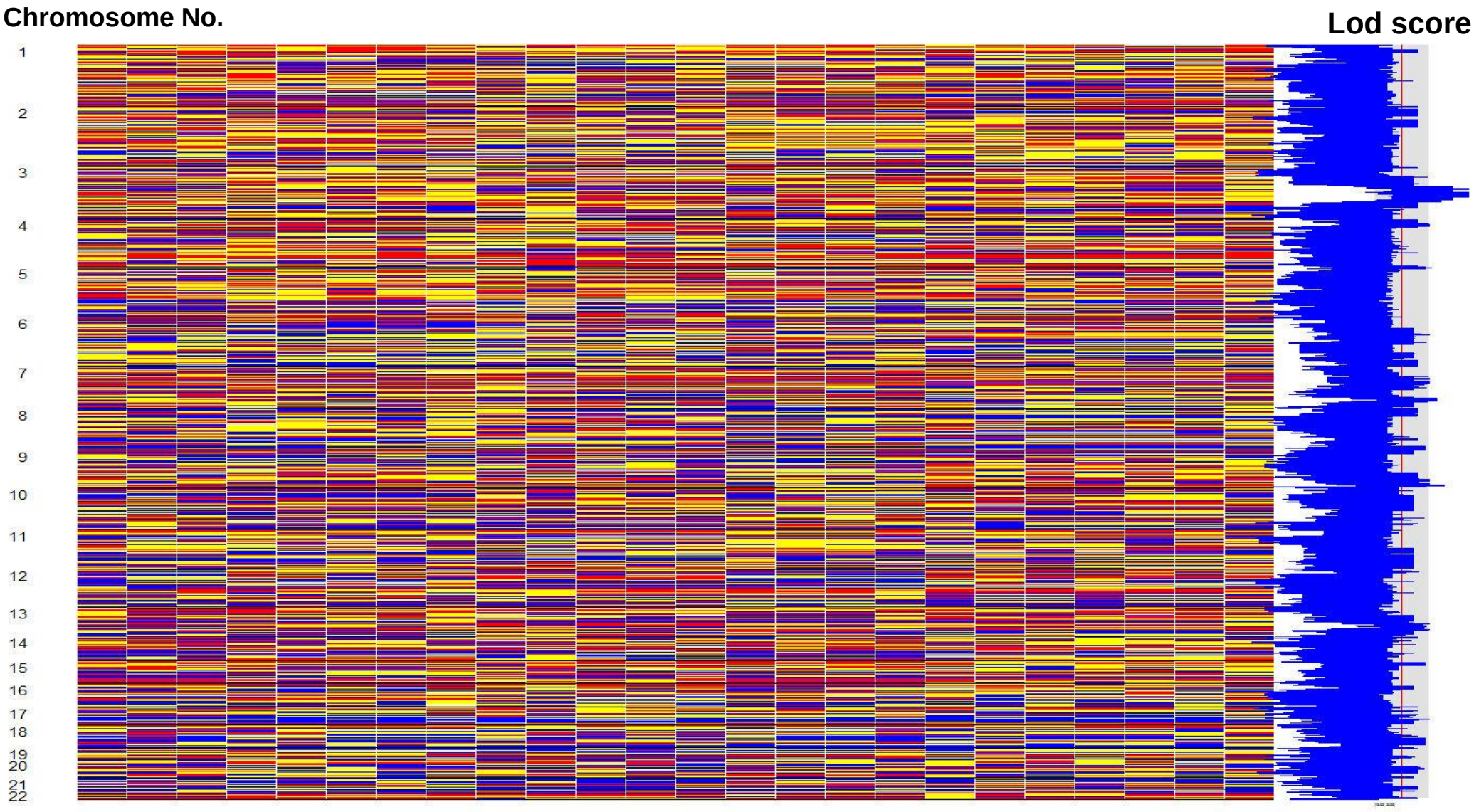
Takashima H, Nakagawa M et al. Ann Neurol 41: 771-780, 1997

Takashima H, Nakagawa M, et al. Neuromuscular Disorders 9: 368-371, 1999

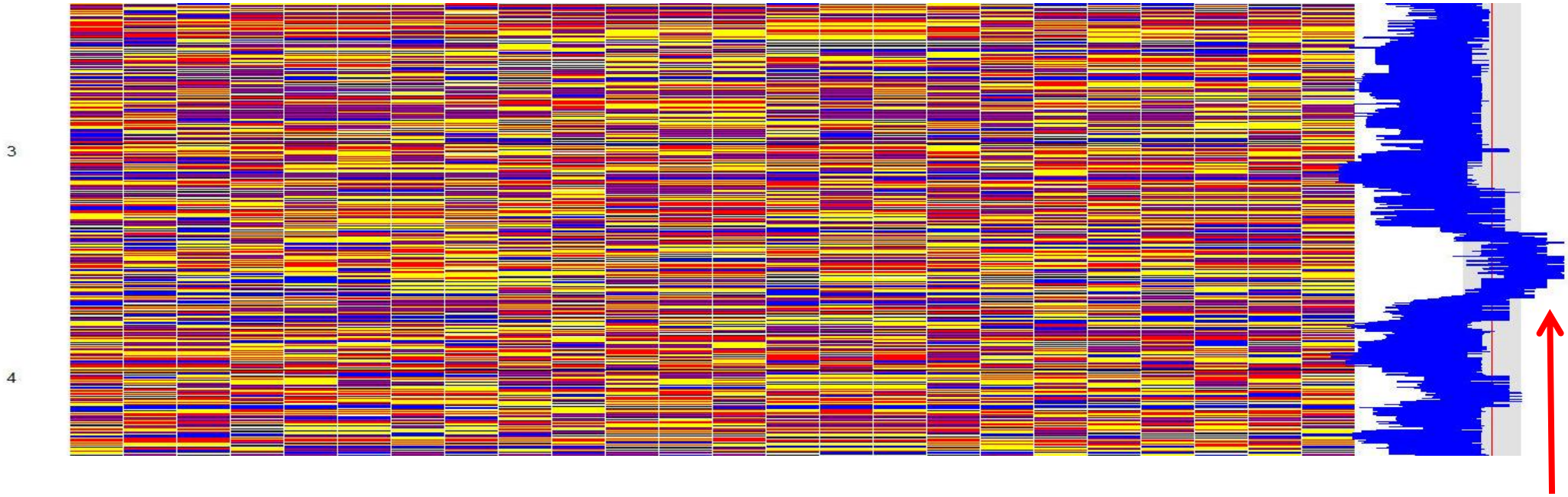
Nakagawa M, Takashima H, et al. Ann NY Acad Sci 883: 449-452, 1999

Maeda K, Kaji R, et al. J Hum Genet 52:907–914, 2007

Whole genome analysis for HMSN-P gene locus using SNP array

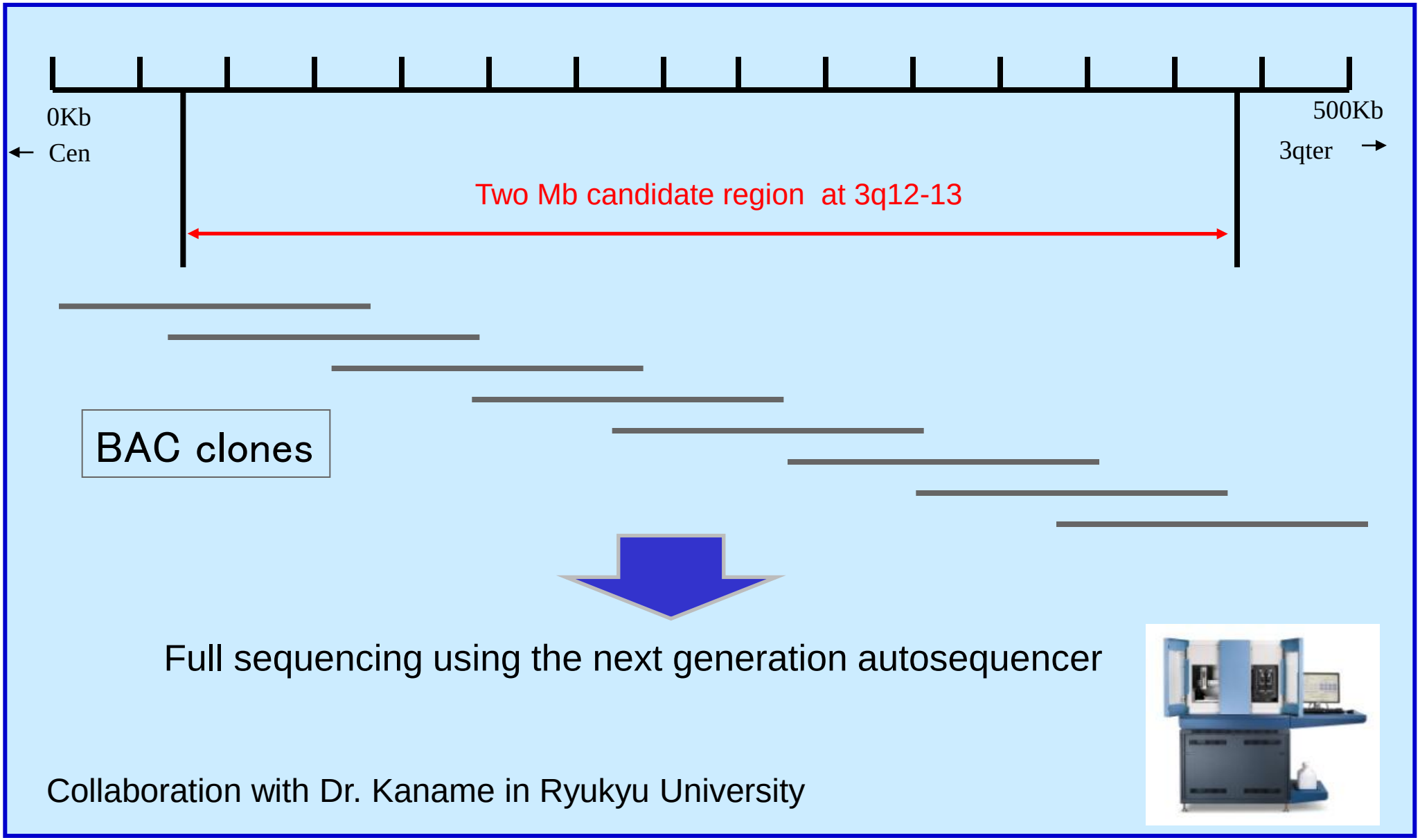


High lod score at centromere region of ch. 3



Several SNPs with LOD>5 are located in 43.8 Mb region at Ch.3.

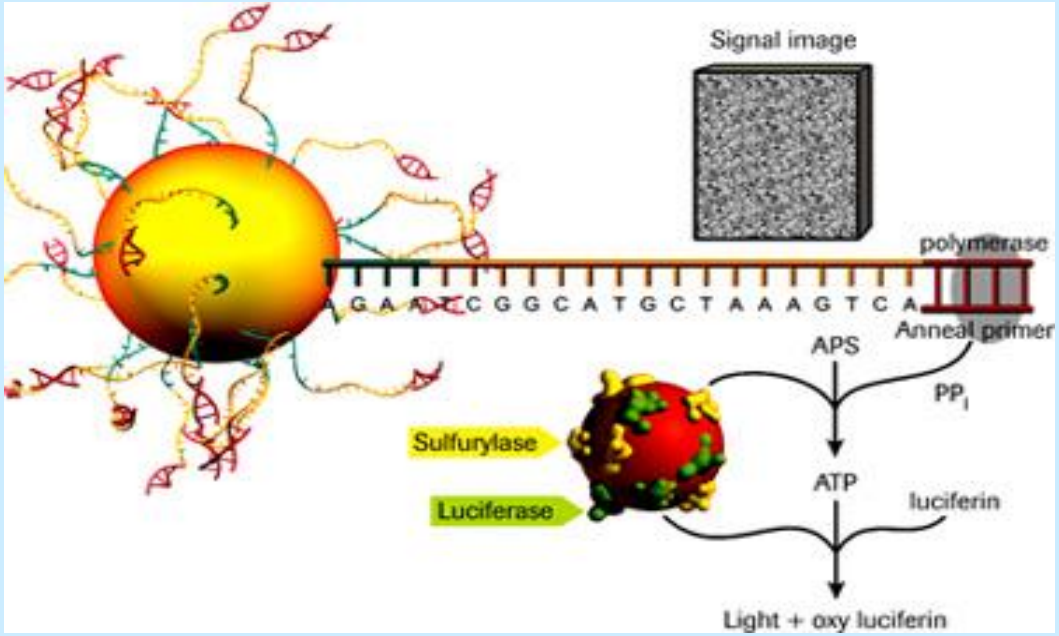
Construction of BAC clone contig derived from HMSN-P patients



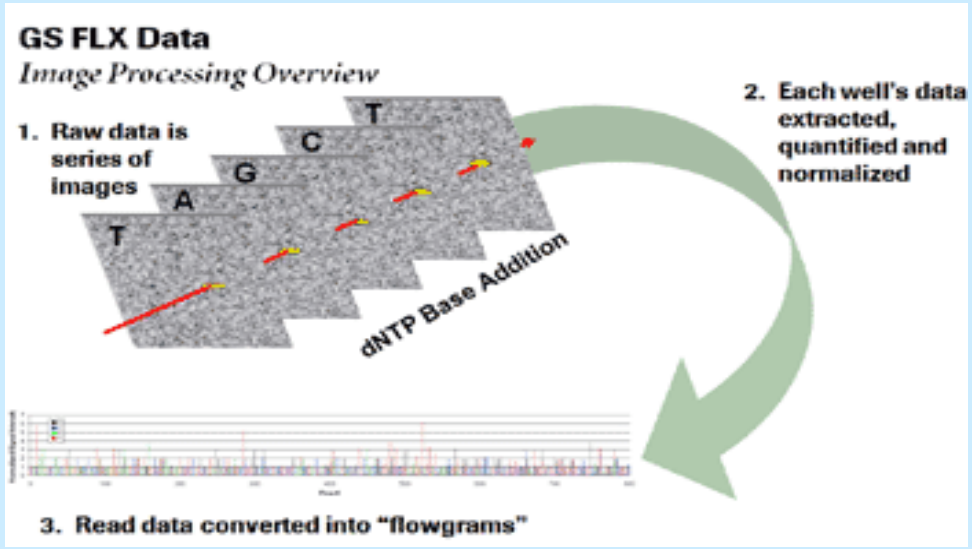
Full sequencing using the next generation autosequencer

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 neuro-pathologists, 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

ALS type	Onset	Inheritance	Locus	Gene	Protein
ALS1	Adult	AD[1]	21q22.1	*SOD1*	Cu/Zn superoxide dismutase
ALS2	Juvenile	AR	2q33-35	*ALS2*	Alsin
ALS3	Adult	AD	18q21	unknown	
ALS4	Juvenile	AD	9q34	*SETX*	Senataxin
ALS5	Juvenile	AR	15q15-21	*SPG11*	Spatacsin
ALS6	Adult	AD[2]	16p11.2	*FUS*	Fused in sarcoma
ALS7	Adult	AD	20p13	unknown	
ALS8	Adult	AD	20q13.33	*VAPB*	VAMP-associated protein B
ALS9	Adult	AD	14q11	*ANG*	Angiogenin
ALS10	Adult	AD	1q36	*TARDBP*	TAR DNA-binding protein
ALS11	Adult	AD	6q21	*FIG4*	PI(3,5)P(2)5-phosphatase
ALS12	Adult	AR/AD	10p15-p14	*OPTN*	Optineurin
ALS-FTD1	Adult	AD	9q21-22	unknown	
ALS-FTD2	Juvenile	AD	9p13.2-21.3	unknown	

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?

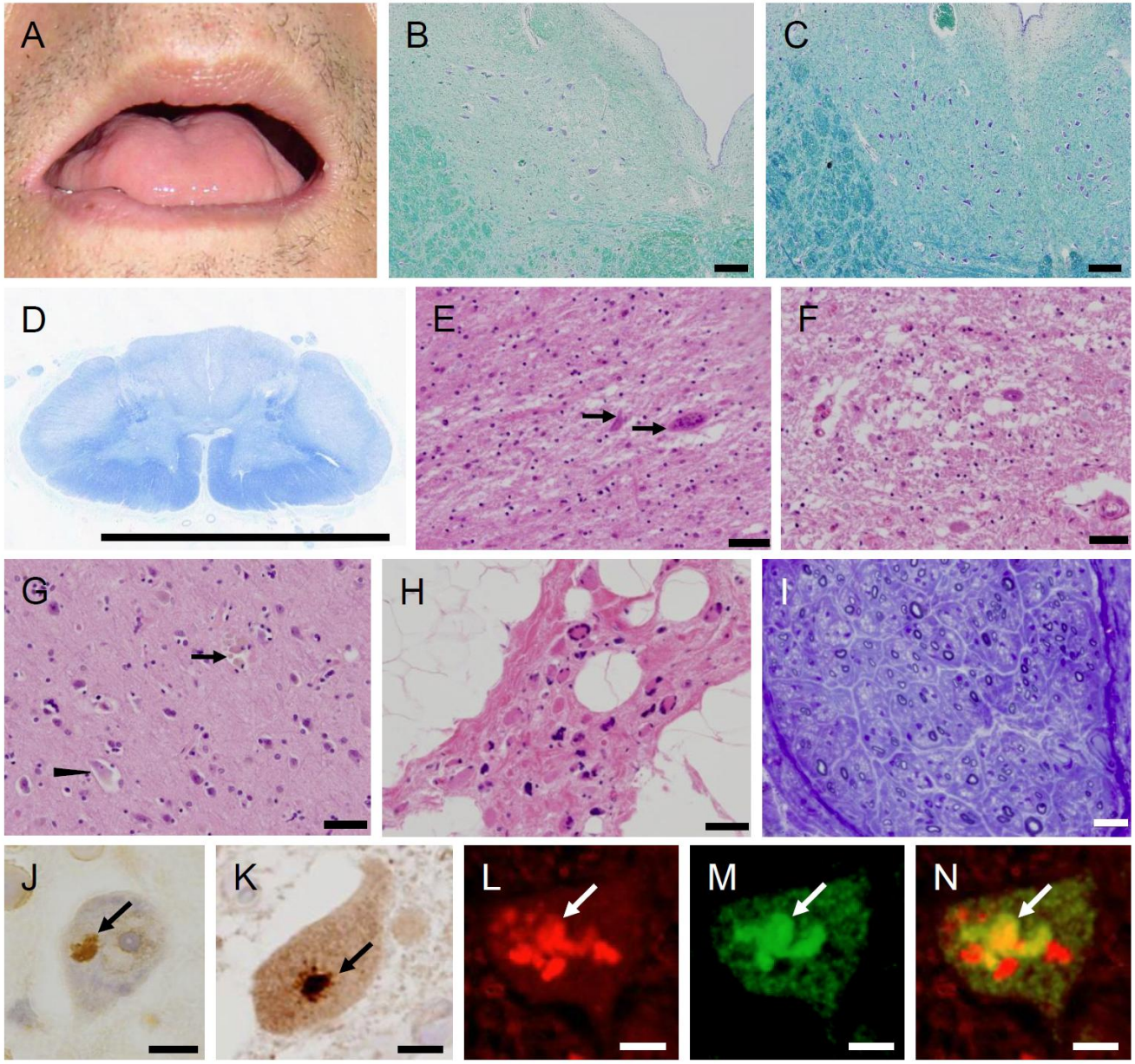
Journal of Neurology, Neurosurgery & Psychiatry (in press)

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

Fujita K[1], Sobue G, Kaji R[1] et al.
[1]Department of Clinical Neuroscience,
The University of Tokushima Graduate School

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)

Is HMSN-P FALS or Nuerpathy?

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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