2.2. Clinical evaluation

For the patients who were admitted after 2009, several neurologists tested their muscle strength and scored the IBM functional rating scale (IBMFRS) [7], which is a widely used scoring system for the functional status of patients with IBM. We evaluated each patient who was admitted before 2008 with IBMFRS scores according to the description in their medical records. In each group, we calculated the ΔIBMFRS/Δtime for an index of progression in functional disabilities, which are the differences in IBMFRS scores between the 2 time points divided by the duration between the 2 time points (years).

2.3. Electrophysiological assessment

In 8 patients with sIBM, the shortest F-wave latency after distal stimulation was recorded in the median, ulnar, tibial, and peroneal nerves. Needle EMG was performed in 12 patients to detect the presence of acute or chronic denervation, or myogenic changes in the deltoid, biceps brachii, or quadriceps femoris muscles. The recordings were obtained using a Neuropack (Nihon Kohden, Tokyo, Japan). Abnormalities in F-wave measurements were defined as a prolongation of the shortest F-wave latency or a lower F-wave frequency. Acute denervation was judged by the presence of a positive sharp wave (PSW), fibrillation potentials (Fib), or fasciculation potentials (Fas). Chronic denervation was determined by an MUP amplitude higher than 1000 μV and its duration longer than 10 ms during weak contraction or by poor recruitment during maximum contraction. Myogenic change was evaluated by an MUP amplitude of less than 200 μV and its duration shorter than 5 ms. All clinicopathological information of each patient were summarized in sTable 1.

2.4. Statistics

We performed statistical evaluations between groups with Mann–Whitney U tests.

3. Results

3.1. Clinical characteristics

Table 1 and sTable 1 illustrate the clinical features of all the patients we evaluated as well as patients in previous reports, which include gender, age at onset, age at diagnosis, pretreatment serum creatine kinase level, treatment, and outcome. The clinical demographics of our 18 patients who met either the defined or possible diagnostic criteria for sIBM established by Hilton-Jones et al., revealed male predominance (83.3%), a mean age of 62.4 years at onset, and a uniform initial symptom of muscle weakness in the upper and/or lower limbs (Table 1).

We categorized the 18 patients into 3 groups based on their age at onset: 2 in the <50 group, 11 in the 50–69 group, and 5 in the ≥70 group (Table 2). In the latter 2 groups, which were typical with regard to age at onset, more than 80% of the patients were male (Table 2). The group with the youngest age at onset had a longer duration between onset and definite diagnosis (biopsy). We next assessed whether progression rates in functional disabilities were different among the 3 groups. We compared ΔIBMFRS/Δtime for an index of the progression of functional disabilities. The ≥70 group had a significantly higher ΔIBMFRS/Δtime ($P = 0.01947$, Mann–Whitney U test), suggesting that progression in functional disabilities of the group with age 70 or more was more rapid (Fig. 1). We also categorized them into 2 groups based on the diagnostic criteria for sIBM established by Hilton-Jones et al.: pathologically defined IBM and clinically defined IBM, or possible IBM. We performed the same consideration with the former 2 groups and the possible IBM group. These 2 groups had no significant differences in their ΔIBMFRS/Δtime (Mann–Whitney U test, data not shown).

3.2. Electrophysiological characteristics

Of our 18 patients with sIBM, 8 and 12 patients were examined by nerve conduction (NC) and needle EMG studies, respectively. We divided those patients into 2 groups: a group with disease duration of less than 12 years, and a group with disease duration of more than 12 years from onset to examination. In the NC study, 4 and 4 patients belonged to the groups with disease duration of less and more than 12 years, respectively. In the needle EMG study, 8 and 4 patients were categorized into the former and latter groups, respectively (sTable 1). Abnormalities in F-waves were frequently detected in the group (75%) with a duration of more than 12 years, whereas no patients in the group with a duration of less than 12 years showed an abnormal F-wave finding (Fig. 2A). All patients showed acute denervation findings, including PSW/Fib in the group with shorter duration, although no patients presented those findings in the group with the longer duration (Fig. 2B). Fas were observed in 12.5% of patients in the group with shorter disease duration, but were not detected in the group with the longer duration (Fig. 2B). Myogenic changes were observed in 62.5% and 50% of patients in the group with the shorter and longer duration, respectively (Fig. 2C). Chronic denervation findings were observed in 75% and 100% of patients in the group with the shorter and longer duration, respectively (Fig. 2D).

Table 1
Clinical summary of our 18 patients diagnosed with sIBM between 1991 and 2013, and comparison between our cases and the cases described in previous reports.Modified from a report by Benveniste et al.

	n	Male dominancy (%)	Age at onset (years)	Age at diagnosis (years)	Creatine kinase level (IU/l)	Patients receiving immunosuppressant (%)	Progression despite therapy (%)
This study	18	83.3	62.4	70.2	646.2	61.1	100
Ringel et al.(1987)	19	79	57.8	62.9			
Lotz et al.(1989)	40	72.5	56.1	62.4	197	72.5	80.2
Sayers et al.(1992)	32	62.5	58	61	1145	87.5	46.4
Beyenburg et al.(1993)	36	58.3	47	53.1	279	44.4	93.75
Lindberg et al.(1994)	18	55.5	60.4	62.7		88.8	75
Amato et al.(1996)	15	86.6	58	64	698	73.3	100
Peng et al.(2000)	78	78.2	56.5				
Felice and North(2001)	35	65.7	64.3	70	444	49	100
Badrising et al.(2005)	64	67.2	57.6		417	35.9	82.6
Benveniste et al. (2011)	136	57.3	61	66	267	52.2	100

IU, international unit.

Table 2
Clinical characteristics in each group categorized by age at onset.

Age at onset (year)	<50	50–69	≥70	Overall
Number of patients	2	11	5	18
Age at onset	43	60.4	74.8	62.4
Gender, male (%)	50.00%	90.90%	80%	83.30%
Patients receiving immunosuppressants (%)	1 (50%)	7	3	11 (61.1%)
Duration between first symptoms and diagnosis, years	17	7.54	4.6	7.8
Pretreatment CK level (IU/l)	254	317.7	1525.8	646.2
Number of patients with inflammatory cellular infiltration into non-necrotic fibers (%)	1 (50%)	9 (81.8%)	3 (60%)	13 (72.2%)
Number of patients with rimmed vacuoles (%)	2 (100%)	11 (100%)	5 (100%)	18 (100%)

CK, creatine kinase; IU, international unit.

4. Discussion

Comparison with the previous cohort studies regarding sIBM cases revealed that the natural histories of our patients with sIBM was similar to those of Western people, as well as those of other Japanese cohorts [2, 8–17]. These observations suggest that the clinical characteristics of sIBM were relatively homogeneous beyond the ethnic differences although people in the United States or Europe with an African origin seem to be less affected with sIBM. In our cohort, the initial diagnoses in more than half of the total patients with sIBM were PM, and the duration to the definite diagnoses was longer than that in the previous reports. Thus, we should keep in mind the possibility of sIBM for aged people with muscle weakness.

In this study, the patients with sIBM with a longer duration frequently showed abnormalities in their F-wave measurements as well as chronic denervation findings. Hokkoku et al. reported that high-amplitude of MUPs can be seen in muscle diseases, especially in the advanced stage of chronic myopathies with hypertrophic fibers such as sIBM [18]. Our observation of F wave abnormalities in the long duration group may suggest conduction impairment at the proximal region including the spinal anterior horns. We assume that aging would be one of the factors that induce chronic denervation as well as F wave abnormalities in long duration groups. In addition, we hypothesized that the pathology of sIBM could affect the lower motor neurons, including the neuromuscular junctions and the spinal anterior roots although we do not have a direct evidence that indicates the involvement of peripheral neuropathy or radiculopathy. Growing evidence suggests that some inherited types of inclusion body myopathy affects not only the skeletal muscles, but also the motor neurons as well as the frontotemporal cortices [19,20]. Thus, a further study would be useful to realize that sIBM pathology involves the motor neurons and/or peripheral neurons, as suggested in literature [4,5].

Fig. 1. ΔIBMFRS/Δtime in each group categorized by age at onset: less than 69 years, and aged 70 or more. In the box and whisker plots, the bottom and top of the box are the first and third quartiles, and the band inside the box is the median. The ends of the whiskers represent the minimum and maximum of all of the data. The asterisk indicates a significance of less than 0.05.

In this study, the oldest group showed a significantly more rapid progression of functional disabilities regarding sIBM. Interestingly, one patient who showed an extremely high value in the ΔIBMFRS/Δtime score had more frequent Fas, compared with other patients in the oldest group. The reason why the patient showed a rapidly progressive course might be the presence of Fas, which strongly suggests on-going denervation. Because the patient had no special reasons that deteriorated the disease course, we should include the patient into the analysis as far as the patient fulfilled the diagnostic criteria for clinically possible IBM.

It is still enigmatic whether inflammation is a primary trigger or a secondary event following muscle degeneration in sIBM pathology. The accumulation of misfolded proteins such as amyloid-like substances and TDP-43 emphasizes the degenerative aspect of the pathophysiological mechanisms of sIBM [21,22]. Moreover, poor responsiveness to immunosuppressants in most cases of sIBM strongly suggests that inflammation does not play a central role in sIBM pathology [23]. In our study, none of our patients showed a substantial recovery of muscle strength, although a few patients showed a transient improvement of serum creatine kinase levels. The patients of case 4 who underwent muscle biopsies twice definitely increased the numbers of RVs (sFig. 1). Thus, the presence of RVs might be related with aging whether the trigger of sIBM is inflammatory cellular infiltration or muscle degeneration.

The principal methodological limitation was the retrospective use of medical records on limited number of patients. Thus, a prospective multicenter study of a large number of patients should be valuable. For understanding of the involvement of motor neurons in sIBM, it would be helpful to analyze the postmortem spinal cord tissues derived from autopsied patients. However, we assume that the clinical characteristics of sIBM are relatively homogeneous beyond the ethnic differences. The group with a younger age at onset had a longer duration between onset and definite diagnosis. The progression of functional disabilities in the group with the older age at onset was more rapid as previously reported [16]. These suggest that aging might be a synergistic factor for the progression of pathology in sIBM, and such age-dependent progression might emphasize the degenerative aspect of pathophysiological mechanisms of sIBM. Further evaluation of how gender-differences and aging could affect clinical findings would be useful for a better understanding of the pathophysiology of sIBM.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2014.08.009.

Conflict of interest

None.

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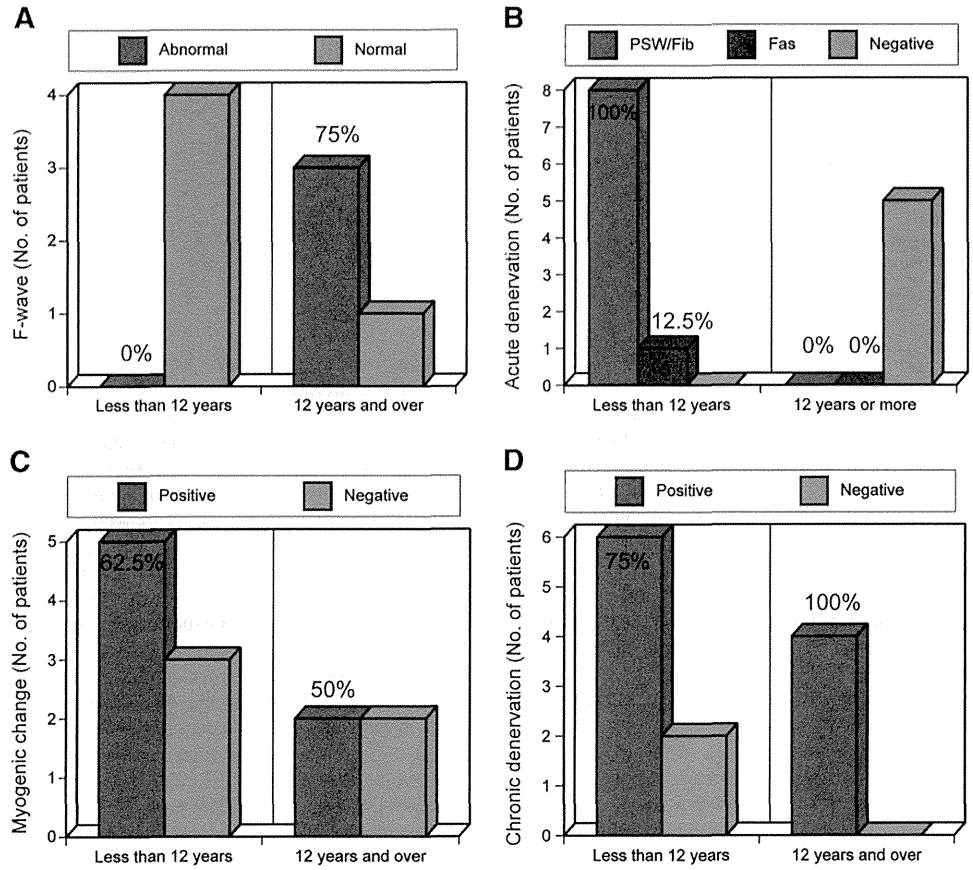

Fig. 2. (A) The number of patients with sIBM who showed abnormal findings in F-wave evaluation in the groups with the disease duration of less than 12 years (left) and 12 or more (right). (B) The number of patients with sIBM who showed acute denervation findings [positive sharp waves (PSW)/fibrillation potentials (Fib) in red, fasciculation potentials (Fas) in blue] in groups with duration of less than 12 years (left) and 12 years or more (right). (C) The number of patients with sIBM who showed myogenic changes in the groups with disease duration of less than 12 years (left) and 12 years or more (right). (D) The number of sIBM patients who showed chronic denervation findings in the groups with duration less than 12 years (left) and 12 years or more (right).

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Scientific correspondence

Clinicopathological features of the first Asian family having vocal cord and pharyngeal weakness with distal myopathy due to a *MATR3* mutation

Distal myopathy is a clinically and pathologically heterogeneous disorder that selectively or disproportionately affects distal muscles of the upper and/or lower limbs [1]. An adult-onset, progressive autosomal dominant distal myopathy that is frequently associated with dysphagia and dysphonia, vocal cord and pharyngeal weakness (VCPDM/MPD2) was recently discovered in a North American and a Bulgarian family; its causative agent being a missense mutation in the *matrin-3 (MATR3)* gene [2,3]. Still, VCPDM remains a fairly rare disease that has only been reported in two families worldwide so far.

According to a previous report on VCPDM, muscle biopsy performed on the quadriceps or gastrocnemius muscles revealed chronic non-inflammatory myopathy with subsarcolemmal rimmed vacuoles (RV) and atrophic fibres, with denervation [2]. Pathologic changes were reported to be more severe in the gastrocnemius than in the quadriceps muscles. Electrophysiological studies have also shown some degree of combination of myogenic and neurogenic changes associated with VCPDM [2].

Here, we report the clinicopathological features of the first Asian family having VCPDM with a missense mutation in the *MATR3* gene. We also examined whether muscle pathology in patients with VCPDM shared histopathological characteristics with other myopathies with RV, including sporadic inclusion body myositis (sIBM), oculopharyngeal muscular dystrophy (OPMD), glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (GNE) myopathy, and valosin-containing protein (VCP) myopathy.

Two Japanese half sisters were examined and summarized in Table 1. Their father noticed a disturbance in his gait in his forties and was dependent on a powered wheelchair in his sixties. He gradually developed respiratory problems and eventually underwent a tracheostomy with mechanical ventilation. He died of respiratory failure at 73.

Case 1, a 44-year-old woman experienced difficulty in ambulation and developed dysphagia of liquid and solids. Upon admission to our hospital, her neurological examination revealed dysphagia and dysarthria, while facial weakness and tongue atrophy were not observed. Moderate muscle weakness was detected in the neck flexor, and mild weakness without fasciculation was observed in the iliopsoas, hamstring, and tibialis anterior muscles. Touch and pinprick sensations were reduced in the distal upper and lower limbs, while vibration and position sense remained intact. Tendon reflexes, especially in the patella tendons, were generally weak.

Case 2, a 68-year-old woman (half sister of the patient in case 1) experienced difficulty in swallowing at age 63 and developed speech difficulty and finger weakness at age 65. Dysphagia and dysarthria progressed gradually until three months before hospital admission. After developing dyspnoea and somnolence, she was admitted to the hospital. Because of her respiratory dysfunction type 2 (PaO_2 50.5 mmHg, $PaCO_2$ 76.7 mmHg) diagnosis, she was treated with non-invasive positive pressure ventilation. Neurological examination showed dysphagia and nasal voice, despite there being no obvious facial weakness or tongue atrophy. Wasting was observed in the bilateral thenar, hypothenar, and first dorsal interossei muscles without fasciculation. The muscle weakness decreased moderately in the wrist extensors, iliopsoas, and extensor hallucis longus muscles and mildly in the deltoid, hamstring, and tibialis anterior muscles. Touch, pinprick, vibration, and position sensations remained intact but slight dysesthesia was present in the toe tips. Tendon reflexes were absent, except of a markedly decreased patella tendons reflex. Both cases of the patients did not fulfil diagnostic criteria of ALS because they lacked upper motor neurone signs.

After obtaining informed consent from patients and approval from a local ethics committee, genomic DNA was extracted from the peripheral blood samples for both patients. We conducted exome-sequencing to determine

Table 1. Summary of clinical data

	Case 1	*Case 2*
Age at biopsy	44	68
Age at onset	40	63
Gender	F	F
Distal weakness		
Legs	+	+
Hands	–	+
Shoulder weakness	–	+
Swallowing dysfunction	+	+
Vocal dysfunction	–	+
Respiratory dysfunction	–	+
CK (U/L, normal ranges: 45–176)	241	81
EMG	Myogenic + neurogenic	Myogenic + neurogenic
NCS	Axonal degeneration type sensorimotor polyneuropathy	Axonal degeneration type motorsensory polyneuropathy
Abnormal lesions in skeletal MRI	Gluteus, quadriceps, hamstring	Paraspinal, gluteus
%FVC (%)	58.9	36.0

the causative mutation for each patient. Exonic sequences were enriched using a SureSelect V4+UTR (Agilent) and subjected to massively parallel sequencing using Illumina Hiseq2000 (100 bp paired-end). Burrows Wheeler Aligner [4] and Samtools [5] were used for alignment and variation detection. It revealed a missense mutation in the *MATR3* gene: p.S85C (c.254C>G), which was exactly the same mutation as described in the only two previous families of VCPDM with a missense mutation in the *MATR3* gene by Senderek *et al.* [3]. Sanger sequencing confirmed this mutation for both cases.

In case 1, the patient underwent biopsy from the left biceps brachii muscle. Haematoxylin and eosin (HE) staining showed a severe fatty change in myofibres of various sizes (Figure 1**a**). Approximately 5% of myofibres presented myopathic changes with RV and internal nuclei (Figure 1**b**,**c**). Inflammatory cellular infiltrates were absent. Acid phosphatase staining showed weak activity consistent with lysosomal activity levels in the RV (Figure 1**d**). ATPase staining showed a predominance of type 1 fibres (Figure 1**e**,**f**). Neither upregulation of major histocompatibility complex (MHC) class I nor cytochrome c oxidase (COX)-negative muscle fibres was observed (data not shown).

In case 2, the patient underwent biopsy from the right biceps brachii muscle. HE staining showed that 1–2% of myofibres presented myopathic changes with RV and internal nuclei (Figure 1**g**,**h**). Inflammatory cellular infiltrates were not observed. Acid phosphatase staining showed no activity (Figure 1**i**). Interestingly, ATPase staining revealed a fibre-type grouping with an increase in type 2 fibres, indicating neurogenic changes (Figure 1**j**–**l**). The specimens showed no upregulation of MHC class I or COX-negative fibres (data not shown).

Electron microscopy of samples from case 1 demonstrated abundant autophagic vacuoles in degenerative myofibres (Figure 1**m**,**n**). As far as we could observe, we found no intranuclear aggregates (Figure 1**n**).

Next, we asked whether myopathic changes associated with VCPDM shared similar histopathological characteristics with myopathies with RV including sIBM, OPMD, GNE myopathy and VCP myopathy. The study was approved by the Ethics Committee of the Kumamoto University Hospital. Recent studies have shown that p62 is the best histological diagnostic marker for sIBM [6–9]. Therefore, we performed immunofluorescence staining using mouse anti-p62/SQSTM1 (1:250; Medical & Biological Laboratories, Nagoya, Japan) and rabbit anti-MATR3 (1:250; Bethyl Laboratories, Montgomery, TX, USA) antibodies. In healthy control subjects, p62 was not detected in normal muscle fibres (data not shown). Immunohistochemical analyses of p62 revealed its sarcoplasmic aggregates in 10–20% of the myofibres in patients with VCPDM (Figure 2**a**,**e**). Substantial immunoreactivity for p62 was observed in myofibres of patients with sIBM (Figure 2**i**), OPMD (Figure 2**m**) as well as GNE myopathy (Figure 2**q**) and VCP myopathy (Figure 2**u**). In healthy control subjects, all myonuclei stained for MATR3 (data not shown).

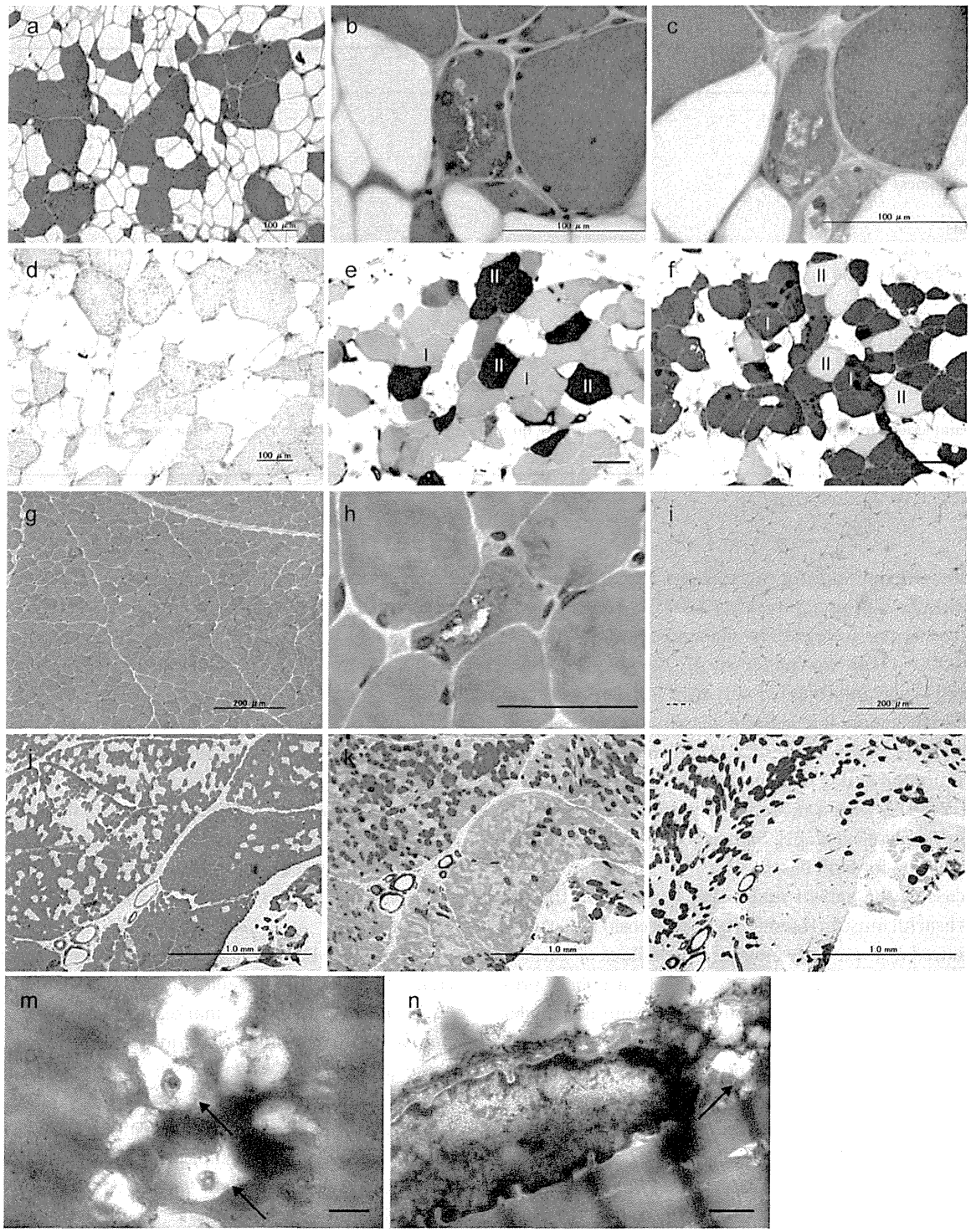

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Figure 1. Muscle histology for the biopsy samples of VCPDM case 1 and 2. (**a–f**) VCPDM case 1: (**a**, **b**) Haematoxylin and eosin (HE) staining at lower (**a**) and higher (**b**) magnifications. (**c**) Modified Gomori-trichrome staining. (**d**) Acid phosphatase staining. (**e**, **f**) ATPase staining at pH 10.6 (**e**), and pH 4.2 (**f**). I and II indicate type 1 and 2 fibres, respectively. Scale bars = 100 μm. (**g–j**) VCPDM case 2: (**g**, **h**) HE staining at lower (**g**) and higher (**h**) magnifications. (**i**) Acid phosphatase staining. (**j–l**) ATPase staining at pH 10.7 (**j**), pH 4.5 (**k**) and pH 4.2 (**l**). Scale bars = 200 μm (**g**, **i**), 50 μm (**h**) and 1.0 mm (**j–l**). (**m**, **n**) Electron microscopic analysis of samples from VCPDM case 1. Arrows indicate autophagic vacuoles. Scale bars = 500 nm (**m**), 800 nm (**n**).

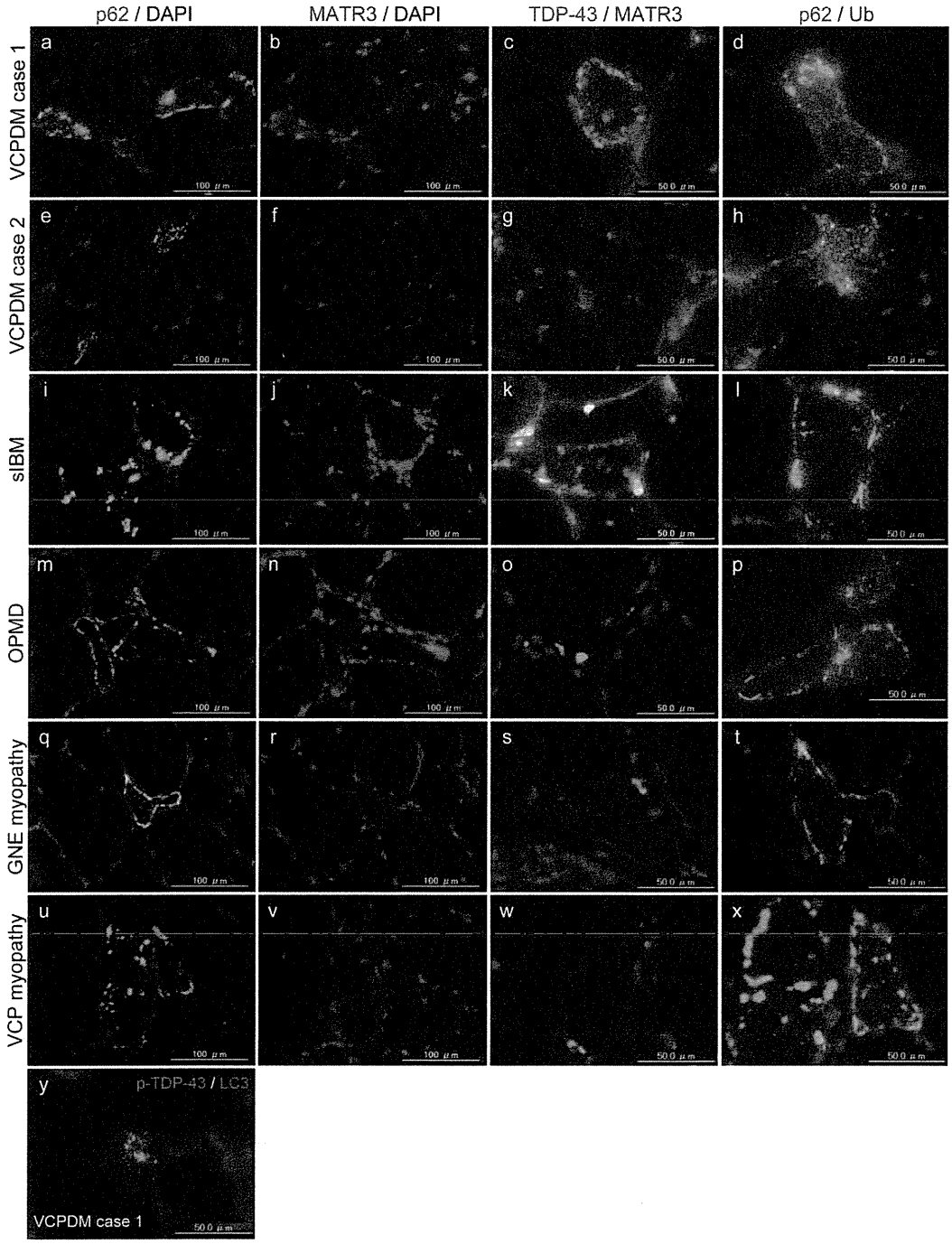

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Figure 2. Immunofluorescence studies for proteins related to myopathies with rimmed vacuoles. Immunofluorescence study of p62 (green; **a**, **e**, **i**, **m**, **q**, **u**) and MATR3 (red; **b**, **f**, **j**, **n**, **r**, **v**) in identical specimens from VCPDM case 1 (**a**, **b**), case 2 (**e**, **f**), sIBM (**i**, **j**), OPMD (**m**, **n**), GNE myopathy with homozygous p.V572L mutation (**q**, **r**), and VCP myopathy with heterozygous p.A232E mutation (**u**, **v**). Double immunofluorescence study of TDP-43 (green) and MATR3 (red) in VCPDM case 1 (**c**), case 2 (**g**), sIBM (**k**), OPMD (**o**), GNE myopathy (**s**) and VCP myopathy (**w**). Double immunofluorescence study of p62 (green) and ubiquitin (red) in VCPDM case 1 (**d**), case 2 (**h**), sIBM (**l**), OPMD (**p**), GNE myopathy (**t**) and VCP myopathy (**x**). Double immunofluorescence study of phosphorylated TDP-43 (green) and LC-3 (red; 1: 500; Medical & Biological Laboratories, Nagoya, Japan) in VCPDM case 1(**y**). Immunolabelled proteins were visualized using anti-mouse immunoglobulin antibody-conjugated Alexa Fluor 488 or anti-rabbit immunoglobulin antibody-conjugated Alexa Fluor 594 (1:200; Life Technologies Corporation, Carlsbad, CA, USA). Scale bars = 100 μm (**a**, **b**, **e**, **f**, **m**, **n**, **q**, **r**, **u**, **v**) and 50 μm (**c**, **d**, **g**, **h**, **k**, **l**, **o**, **p**, **s**, **t**, **w**, **x**, **y**). Nuclei were stained with 4′, 6-diamidino-2-phenylindole (blue).

Table 2. Semi-quantitative analysis for immunohistochemistry

	p62	*MATR3*	*TDP-43*	*Ubiquitin*
VCPDM Case 1	++, aggregates	+, granular or loss of nuclear staining	++, aggregates	+, granular
VCPDM Case 2	++, aggregates	+, granular or loss of nuclear staining	±, diffuse	+, granular
sIBM	++, aggregates	±, granular	++, aggregates	+, granular
OPMD	++, aggregates	±, granular	++, aggregates	+, granular
GNE myopathy	++, aggregates	±, granular or loss of nuclear staining	+, aggregates	+, granular
VCP myopathy	++, aggregates	±, granular or loss of nuclear staining	++, aggregates	+, granular

VCPDM, vocal cord and pharyngeal weakness with distal myopathy; sIBM, sporadic inclusion body myositis; OPMD, oculopharyngeal muscular dystrophy. –, no positive cells; ±, occasional positive cells; +, moderate numbers of positive cells; ++, frequent numbers of positive cells.

Immunohistochemical analysis of MATR3 demonstrated sarcoplasmic granular staining in p62-positive degenerating myofibres for case 1 (Figure 2**b**). Some myonuclei showed a loss in immunoreactivity for MATR3 (Figure 2**b**). In case 2, some myonuclei presented immunoreactivity loss for MATR3 without sarcoplasmic staining (Figure 2**f**). Sarcoplasmic granular staining for MATR3 was observed in some p62-positive degenerating myofibres of patients with sIBM (Figure 2**j**), OPMD (Figure 2**n**), and GNE (Figure 2**r**) and VCP (Figure 2**v**) myopathies. Notably, most myonuclei remained strongly reactive to MATR3 in sIBM and OPMD, (Figure 2**j**,**n**) whereas some myonuclei showed a loss in immunoreactivity for MATR3 in GNE (Figure 2**r**) and VCP (Figure 2**v**) myopathies.

We then examined whether other proteins involved in RV-related myopathies accumulated in the myofibres of patients with VCPDM. Previous studies have shown frequent accumulation of TAR DNA-binding protein 43 kDa (TDP-43) in sarcoplasmic granules within degenerating myofibres of patients with sIBM (Figure 2**k**), OPMD (Figure 2**o**) and GNE (Figure 2**s**) and VCP (Figure 2**w**) myopathies. Within myofibres with TDP-43-immunoreactive sarcoplasmic aggregates, nuclei were less immunoreactive for TDP-43 in patients with sIBM (Figure 2**k**). An immunohistochemical analysis using mouse anti-TDP-43 (1: 250; ProteinTech Group, Chicago, IL, USA) antibody demonstrated the presence of its sarcoplasmic aggregates (~10%) in myofibres for Case 1 (Figure 2**c**) and diffuse cytoplasmic staining in myofibres for Case 2 (Figure 2**g**). In myofibres with TDP-43-positive aggregates in Case 1, myonuclei were less immunoreactive for both TDP-43 and MATR3, although both proteins did not necessarily colocalize (Figure 2**c**). Interestingly, some TDP-43-positive granules were immunoreactive for mouse anti-phosphorylated TDP-43 (pS409/410) (1: 3000; Cosmo Bio, Tokyo, Japan) antibody (Figure 2**y**).

Because a deficit in protein degradation machinery is suspected to be one of the pathophysiological mechanisms underlying RV-related myopathies, we investigated the involvement of ubiquitin in the myofibres of patients with VCPDM, using rabbit anti-ubiquitin (1: 200; Dako) antibody. In these patients, immunohistochemistry for ubiquitin showed sarcoplasmic granular staining mainly in p62-positive fibres (Figure 2**d**,**h**). Sarcoplasmic granular staining for ubiquitin was also observed in sIBM (Figure 2**l**), OPMD (Figure 2**p**) as well as GNE (Figure 2**t**) and VCP (Figure 2**x**) myopathies. Expression profiles are summarized in Table 2.

We herein reported clinicopathological features of the first Asian family having VCPDM with a missense mutation in the *MATR3* gene: p.S85C (c.254C>G), which was a sole mutation that has been described in the previous cases with VCPDM. Collectively, our results showed intrafamilial variation including the presentation of motorsensory neuropathy. We identified the histopathological characteristics of VCPDM: myopathic changes with RV but no inflammatory infiltrate, neurogenic changes, diffuse sarcoplasmic distribution of MATR3 and/or loss of nuclear staining, and other histological features common to RV-myopathies, such as accumulation of p62, TDP-43 and ubiquitin.

According to a previous report on the clinical features of VCPDM [2], muscle weakness is exhibited asymmetrically in the feet and ankles and/or the hands. The distribution of weakness in the lower limbs has been more affected in the peroneal muscles than in the gastrocnemius muscles. Weakness in the upper limbs occurs more often in the finger extensors and abductor pollicis brevis

(APB), and to lesser extent in the deltoid muscles. While vocal cord and pharyngeal weakness can be present at the onset of the distal weakness, some patients show neither vocal cord dysfunction nor problems swallowing. Our skeletal muscle MRI data indicated that the quadriceps muscles were relatively spared. Of note, the sparing of the vastus lateralis was described in another distal myopathy with RV, such as GNE myopathy [10], and the similarity might suggest the common pathogenesis between the both diseases.

Muscle histology in patients with VCPDM has previously revealed chronic non-inflammatory myopathy in addition to the presence of RV, usually in subsarcolemmal as well as atrophic fibres [2]. However, the specific characteristics of VCPDM have still not been conclusively determined. TDP-43 has been identified as a major component protein of ubiquitin-positive inclusions in the brains of patients with frontotemporal lobar degeneration with ubiquitin-positive inclusions and in the spinal anterior horns of patients with amyotrophic lateral sclerosis (ALS) [11,12]. TDP-43-positive granules have been observed not only in sIBM but also in other vacuolar myopathies such as OPMD, and VCP and GNE myopathies [7,13–17]. Our observation of TDP-43-positive granules in VCPDM suggests that the presence of TDP-43-positive aggregates may be a common phenomenon among myopathies associated with RV [8,13,14,17,18].

MATR3 is a component of the nuclear matrix and thought to be associated with the protein machinery for transcription, RNA splicing and DNA replication [3]. To date, the mutation of p.S85C (c.254C>G) in the *MATR3* gene is a sole mutation described in the previous cases with VCPDM. Recent exome-sequencing study has revealed mutations in the *MATR3* gene in some of ALS kindreds [19]. Interestingly, the report included one of the families harbouring the S85C mutation that had been originally described as having myopathy due to the *MATR3* mutation [3], and reclassified the condition as slowly progressive familial ALS. However, we provide definite evidence that the S85C *MATR3* mutation actually induced distal myopathy with minor neurogenic features. Taken together with these observations, the *MATR3* mutation can indeed cause wide-ranged phenotypes from inclusion body myopathy to motor neurone disease.

Although MATR3 is a multifunctional protein [19], the effect of the mutation on structure and function of MATR3 protein remains unsolved. Our observation of the sarcoplasmic accumulation of p62, TDP-43, and ubiquitin suggests a deficit in protein degradation, possibly due to ubiquitin proteasome system dysfunction and/or autophagy. Furthermore, the findings that immunoreactivity loss for MATR3 in the myonuclei was related with its sarcoplasmic staining might suggest that the mutation in the *MATR3* gene interferes directly or indirectly with the protein localization resulting in loss-of-function. The dysfunction of MATR3 by its mutation would possibly lead to a modification in gene expression related to abnormal chromatin organization, deregulation of nuclear mRNA export, abnormal pre-mRNA splicing, or nuclear proteome alterations in skeletal muscles. As *MATR3* knockdown caused deficit in the machinery for DNA damage response and cell cycle [20], such a nuclear dysfunction might be involved in VCPDM pathogenesis. Further investigation and establishing an understanding of the *MATR3* mutation in transgenic animals will be necessary to elucidate the pathophysiological mechanisms underlying myofibre degeneration and neuropathic change.

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Authors' contribution

SY and AM: conception, design, acquisition of data, analysis and interpretation. YN, RK, NT, TN, YM, HU, SI, YH, AH, IH, SM and JY: acquisition of data. MU, HT and ST: acquisition of data and critical revision of the manuscript for important intellectual content. AY: analysis and interpretation, critical revision of the manuscript for important intellectual content and study supervision.

Conflict of interest

The authors declare that they have no conflict of interest.

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平成 26 年度　班会議プログラム

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希少難治性筋疾患に関する調査研究班
(H26-難治等（難）-一般-079)

「　ＩＢＭ分科会　」
H26 年度 会議プログラム

研究代表者　東北大学大学院医学系研究科　神経内科学

青木　正志

日　　時　　平成 27 年 2 月 6 日(金) 11:00～12:30

会　　場　　都市センターホテル　706 会議室

東京都千代田区平河町 2-4-1

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開会挨拶　　11:00～11:03　　研究代表者　　青木 正志

《 Session I 》　11:03～11:20

診断基準の再検討について　　鈴木 直輝

封入体筋炎に関する班員研究発表

《 Session II 》11:20～11:53　　座　　長　　村田 顕也

1.孤発性封入体筋炎における抗 NT5C1A 抗体測定の意義と病態への関与に関する検討

研 究 分 担 者：山下　賢
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研究協力者所属：熊本大学大学院生命科学研究部　神経内科学分野

2. 封入体筋炎としては非典型的な臨床経過を呈した抗 cN1A 抗体陽性の炎症性筋疾患 6 例

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3) 同　トランスレーショナルメディカルセンター

3. 当院蓄積症例による IBM と HTLV-1 感染との関連についての研究

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2) 鹿児島大学大学院医歯学総合研究科　神経内科・老年病学

《 Session III 》 11:53～12:26　　座　　長　山下 賢

4.骨格筋再生過程における Myostatin および関連蛋白の検討

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研究協力者所属：和歌山県立医科大学　神経内科学講座

5. 封入体筋炎における選択的オートファジー

研 究 分 担 者：日下博文
所　　属：関西医科大学　神経内科
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研究協力者所属：1) 大阪市立総合医療センター　神経内科
2) 関西医科大学　神経内科

6. 骨 Paget 病と痙性対麻痺を併発した VCP 遺伝子変異によるミオパチーの１例

研 究 分 担 者：梶　龍兒
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閉会挨拶　　12:26～12:30　　研究代表者　　青木 正志

厚生労働科学研究費補助金（難治性疾患等政策研究事業(難治性疾患政策研究事業)）

希少難治性筋疾患に関する調査研究班
(H26-難治等（難）-一般-079)

H26 年度 班会議プログラム

研究代表者　東北大学大学院医学系研究科　神経内科学

青木　正志

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会　　場　　都市センターホテル　706 会議室

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開会挨拶　　13:00 ～ 13:03　　研究代表者　青木 正志

13:03 ～ 13:15

本研究班の目的・展望と封入体筋炎分科会の活動状況　　青木 正志

《 Session I 》13:15 ～ 14:15　　座　長　林 由起子

1. 本邦における骨格筋チャネル病の実態について－重症度分類および診断ガイドラインに向けて－

研 究 分 担 者：○高橋正紀(たかはし　まさのり)
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2. 本邦における先天性筋無力症候群

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3. 封入体筋炎ではC型肝炎ウイルス既感染率が高い

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4. 自己貪食空胞性ミオパチーの診療実態と診療ガイドライン作成の試み

研 究 分 担 者：○杉江和馬(すぎえ　かずま)
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4) 奈良県立医科大学　循環器・腎臓・代謝内科

《 Session II 》14:15 ～ 15:00　　座　　長　　西野　一三

5. Schwaetz-Jampel 症候群の病態解明と調査

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2) 名古屋大学大学院医学系研究科神経遺伝情報学

6. 先天性ミオパチーの診断基準と診断のための評価法の検討

研 究 分 担 者：小牧宏文
所　　属：国立精神・神経医療研究センター病院　小児神経科
研 究 協 力 者：○石山昭彦(いしやま　あきひこ)
研究協力者所属：国立精神・神経医療研究センター病院　小児神経科

7. マリネスコ・シェーグレン症候群の実態調査結果

研 究 分 担 者：○林　由起子(はやし　ゆきこ) 1)2)3)
所　　属：東京医科大学病態生理学分野
研 究 協 力 者：後藤正英 4)5)、後藤加奈子 2)3)、小牧宏文 4)、西野一三 2)3)
研究協力者所属：1)東京医科大学病態生理学分野
2)国立精神・神経医療研究センター神経研究所疾病研究第一部
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4)国立精神・神経医療研究センター病院小児神経科
5)自治医科大学小児科

閉会挨拶　　15:00　　研究代表者　　青木　正志