




## RESEARCH ARTICLE

# Nationwide survey of patients with multisystem proteinopathy in Japan

Satoshi Yamashita<sup>1,2</sup> , Yuji Takahashi<sup>3</sup>, Jun Hashimoto<sup>4</sup>, Ayuka Murakami<sup>5</sup>, Ryoichi Nakamura<sup>5,6</sup>, Masahisa Katsuno<sup>5,7</sup> , Rumiko Izumi<sup>8</sup> , Naoki Suzuki<sup>8</sup>, Hitoshi Warita<sup>8</sup>, Masashi Aoki<sup>8</sup> & the Japan MSP Study Group\*

<sup>1</sup>Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

<sup>2</sup>Department of Neurology, International University of Health and Welfare Narita Hospital, Narita, Japan

<sup>3</sup>Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

<sup>4</sup>Department of Orthopaedic Surgery, National Hospital Organization Osaka Minami Medical Center, Osaka, Japan

<sup>5</sup>Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan

<sup>6</sup>Department of Neurology, Aichi Medical University School of Medicine, Nagakute, Aichi, Japan

<sup>7</sup>Department of Clinical Research Education, Nagoya University Graduate School of Medicine, Nagoya, Japan

<sup>8</sup>Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Japan

## Correspondence

Satoshi Yamashita, Department of Neurology, International University of Health and Welfare Narita Hospital, 852 Hatakeda, Narita, Chiba 286-8520, Japan. Tel: +81-476-35-5600; Fax: +81-476-35-5586; E-mail: [y-stsh@iuhw.ac.jp](mailto:y-stsh@iuhw.ac.jp)

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## Abstract

**Objective:** Multisystem proteinopathy (MSP) is an inherited disorder in which protein aggregates with TAR DNA-binding protein of 43 kDa form in multiple organs. Mutations in *VCP*, *HNRNPA2B1*, *HNRNPA1*, *SQSTM1*, *MATR3*, and *ANXA11* are causative for MSP. This study aimed to conduct a nationwide epidemiological survey based on the diagnostic criteria established by the Japan MSP study group. **Methods:** We conducted a nationwide epidemiological survey by administering primary and secondary questionnaires among 6235 specialists of the Japanese Society of Neurology. **Results:** In the primary survey, 47 patients with MSP were identified. In the secondary survey of 27 patients, inclusion body myopathy was the most common initial symptom (74.1%), followed by motor neuron disease (11.1%), frontotemporal dementia (FTD, 7.4%), and Paget’s disease of bone (PDB, 7.4%), with no cases of parkinsonism. Inclusion body myopathy occurred most frequently during the entire course of the disease (81.5%), followed by motor neuron disease (25.9%), PDB (18.5%), FTD (14.8%), and parkinsonism (3.7%). Laboratory findings showed a high frequency of elevated serum creatine kinase levels and abnormalities on needle electromyography, muscle histology, brain magnetic resonance imaging, and perfusion single-photon emission computed tomography. **Interpretation:** The low frequency of FTD and PDB may suggest that FTD and PDB may be widely underdiagnosed and undertreated in clinical practice.

## Introduction

Multisystem proteinopathy (MSP) is an inherited disorder in which protein aggregates with TAR DNA-binding protein 43 kDa (TDP-43) are formed in multiple organs, including skeletal muscle, bone, and the central nervous system. Various combinations of inclusion body myopathy (IBM), Paget’s disease of bone (PDB), and frontotemporal dementia (FTD) were previously referred to as inclusion body myopathy with Paget’s disease and

frontotemporal dementia (IBMPFD).<sup>1</sup> In 2004, haplotype analysis of families with IBMPFD revealed that mutations in the *valosin-containing protein* (*VCP*) gene are responsible for the disease.<sup>2</sup> Furthermore, mutations in the *VCP* gene have been reported to cause a familial form of amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND).<sup>3</sup> IBMPFD includes not only IBM, PDB, and FTD, but also ALS and Parkinson’s disease (PD), as well as various neuromuscular diseases; a more comprehensive concept of MSP has been proposed.<sup>4,5</sup> In addition to the

*VCP* gene, mutations in *HNRNPA1*, *HNRNPA2B1*, *SQSTM1*, *MATR3*, and *ANXA11* genes have been identified as causes of MSP.<sup>6</sup>

The function of proteins encoded by the causative genes can be broadly classified into ubiquitin-related proteolysis, calcium-binding proteins, and RNA-binding proteins. However, variants in genes encoding RNA-binding proteins have been identified in various neuromuscular degenerative diseases, which may be included in MSP in the future, further expanding the disease concept. However, international consensus on the disease concept of MSP is still lacking, and diagnostic criteria have not been established, making the diagnosis of MSP in cases without typical symptoms difficult. In addition, epidemiological and natural history information based on an accurate diagnosis is not available, making it difficult to conduct the clinical studies necessary to establish new treatments.

The purpose of this study was to clarify the actual status of MSP patients in Japan by conducting epidemiological surveys throughout Japan based on certain clinical diagnostic criteria and comparing the results with clinicopathological characteristics identified by international research groups.

## Methods

### Patients

To conduct a nationwide epidemiological survey, we first established the inclusion criteria for and categories of MSP, with an orthopedic specialist (Tables 1–S6). We enrolled the patients who fulfilled the categories of “MSP with two or more phenotypes,” “MSP with only one phenotype,” or “MSP without a known genetic cause” into the study. Informed consent was obtained verbally from all participants following the Declaration of Helsinki for the use of clinical records for research purposes. The work was approved by the local institutional review boards and ethics committees of Kumamoto University Hospital (Genome no. 487).

### Primary and secondary epidemiological surveys

A primary questionnaire survey was conducted among 6235 Japanese Neurological Society specialists (as of June 2021). The survey was conducted by paper mail over 10 months. Those who had not responded to the initial survey were reminded by mail in the sixth month of the survey to increase the number of survey responses. We obtained the entry date, institution and department name, responding physician’s name, and presence of cases that met criteria of “MSP with two or more phenotypes,”

“MSP with only one phenotype,” or “MSP without a known genetic cause,” or presence of cases with known mutations of related genes (*VCP*, *HNRNPA2B1*, *HNRNPA1*, *SQSTM1*, and *MATR3*) that did not meet the criteria for MSP from 2016 to 2020. We requested the respondents to check “no” even if they have no patients with MSP to estimate the number of patients with the disease nationwide.

For the secondary questionnaire survey of MSP, we obtained sex, date of birth, current age, categories, presumed date of onset, date of diagnosis, status of medical treatment (mainly hospitalized, mainly outpatient, hospitalized/outpatient, transferred to hospital, deceased, or others), consanguinity of parents, presence of disease development in relatives, initial symptoms (FTD, MND, IBM, PDB, parkinsonism, or others), clinical symptoms during the entire course, examination findings on brain computed tomography and magnetic resonance imaging, brain perfusion single-photon emission computed tomography, needle electromyography, serum creatine kinase levels, muscle histology, alkaline phosphatase (ALP) and bone ALP tests, bone x-ray and scintigraphy, bone histology, dopamine transporter scintigraphy, and metaiodobenzylguanidine myocardial scintigraphy, genetic testing (*VCP*, *HNRNPA2B1*, *HNRNPA1*, *SQSTM1*, *MATR3*, and others), treatments, and severity at the initial examination, and follow-up consultation.

### Statistical analysis

Data are expressed as median (25% and 75% percentile) for non-normal distribution. Differences in clinical characteristics among genetic mutations were analyzed using the Kruskal–Wallis nonparametric analysis of variance with Dunn’s multiple comparisons tests, or chi-squared, and Fisher’s exact tests. All analyses were conducted using Prism 8 software (GraphPad Software Inc., San Diego, CA, USA).

## Results

### Patients with MSP in Japan based on a nationwide epidemiological survey

We conducted a primary survey of 6235 specialists affiliated with the Japanese Society of Neurology and received responses from 1119 (17.9%) specialists as of 31 March 2022. A total of 47 MSP cases were reported: 12 “MSP with two or more phenotypes,” 22 “MSP with only one phenotype,” and 11 “MSP without a known genetic cause,” and 2 non-MSP-related genetic variants.

We next conducted a secondary survey through the mail. Responses were received from 19 specialists

(61.3%), collecting information on 27 out of 47 (57.4%) cases. Clinical characteristics of the patients included a median age of 50.0 years at onset (Fig. 1A, Table S7), a median age of 59.0 years at diagnosis (Fig. 1B, Table S7), and a median age of 65.0 years at last follow-up (Fig. 1C, Table S7). The categories were “MSP with two or more phenotypes” in 7 patients (25.9%), MSP with only one phenotype” in 17 patients (63.0%), and MSP without a known genetic cause” in 3 patients (11.1%) (Fig. 1D, Table S7). With regard to the status of medical treatments, 15 patients (55.5%) were outpatients at the hospital where they were diagnosed, 8 (29.6%) were transferred to other hospitals, 5 (18.5%) were repeatedly inpatient and outpatient, 1 (3.7%) was primarily hospitalized, and 2 (7.4%) died. Cases with known family history were observed in 81% of the patients (Fig. 1E).

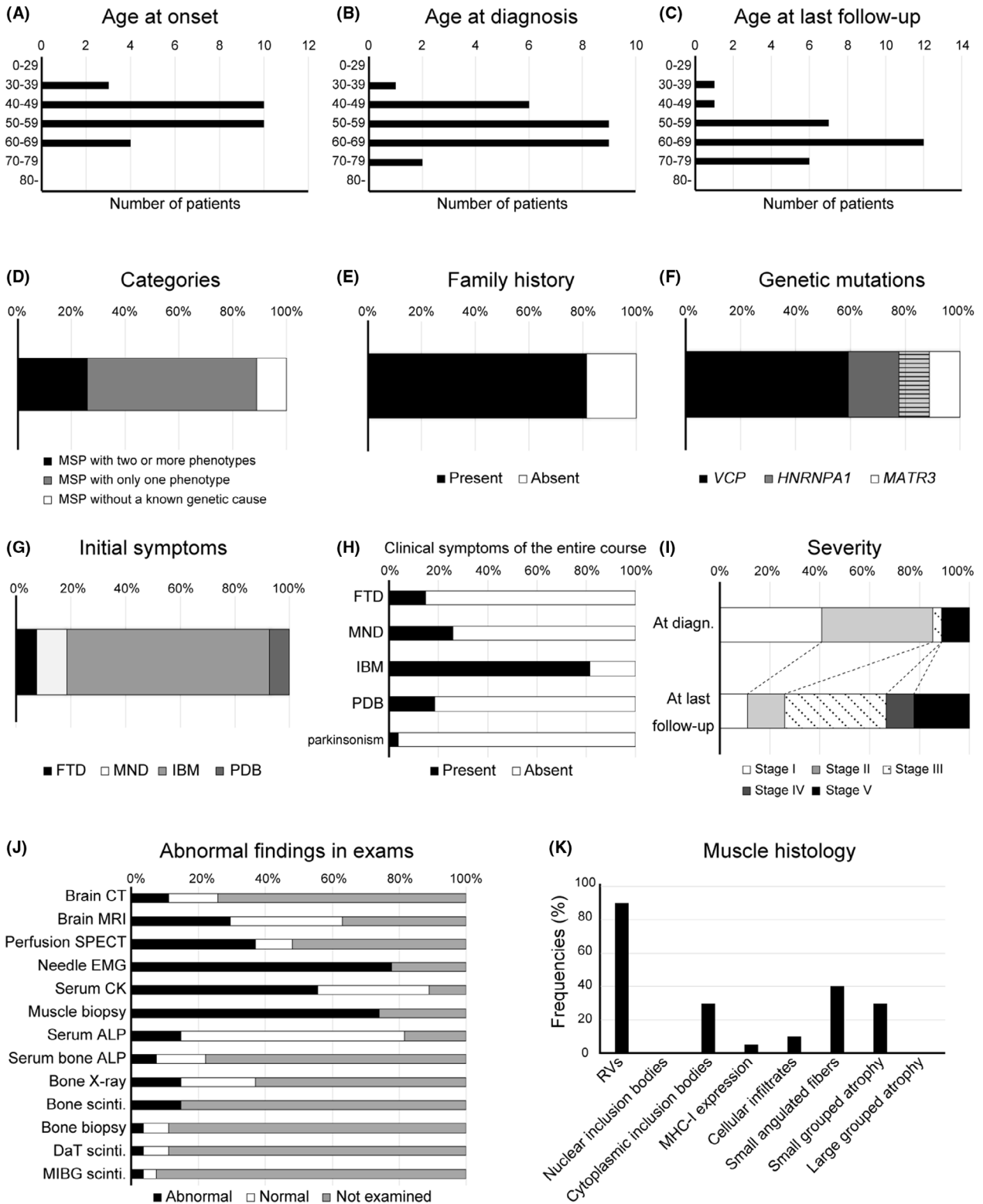
Genetic variants were detected in 24/27 patients (88.9%): *VCP* in 16 patients (59.3%), *HNRNPA1* in 5 patients (18.5%), and *MATR3* in 3 patients (11.1%) (Table S8). No known MSP-related gene mutations were detected in three patients (11.1%) (Fig. 1F, Table S7). The most common initial symptoms were IBM (74.1%), followed by MND (11.1%), FTD (7.4%), and PDB (7.4%), with no cases of parkinsonism (Fig. 1G, Table S7). IBM occurred most frequently during the entire course of the disease (81.5%), followed by MND (25.9%), PDB (18.5%), FTD (14.8%), and parkinsonism (3.7%) (Fig. 1H, Table S7).

Myopathy was reported in 22 out of 27 patients, with a mean age of onset of 50.1 years (range: 39–65 years). Muscle atrophy was absent in the face, but was present in 6 patients (27.3%) in the shoulder girdle, 6 (27.3%) in the upper arm, 16 (72.7%) in the limb-girdle, 13 (59.1%) in the thigh, 4 (18.2%) in the distal upper limb, 6 (27.3%) in the distal lower limb, and 2 (9.1%) in the neck muscles. MND was found in 7 out of 27 patients, with a mean age of onset of 56.3 years (range: 35–68 years). No patient had upper motor neuron (UMN) signs in the cranial region. However, UMN signs were identified in 2 (28.6%) patients in the cervical spinal cord region, 1 (4.1%) patient in the thoracic spinal cord region, and 5 (71.4%) patients in the lumbosacral spinal cord region. Lower motor neuron (LMN) signs were found in 1 (14.3%) patient in the cranial region, 4 (57.1%) patients in the cervical spinal cord region, 3 (42.9%) patients in the thoracic spinal cord region, and 5 (71.4%) patients in the lumbosacral spinal cord region. Both UMN and LMN signs were clinically impaired in 4 of the 7 cases, only UMN signs were impaired in 1 case, and only LMN signs were impaired in 2 cases. PDB was reported in 5 out of 27 patients, with a mean age of onset of 56.2 years (range: 51–61 years). PDB was found in 5 of 16 patients (31.3%) with *VCP* mutations, but none of the

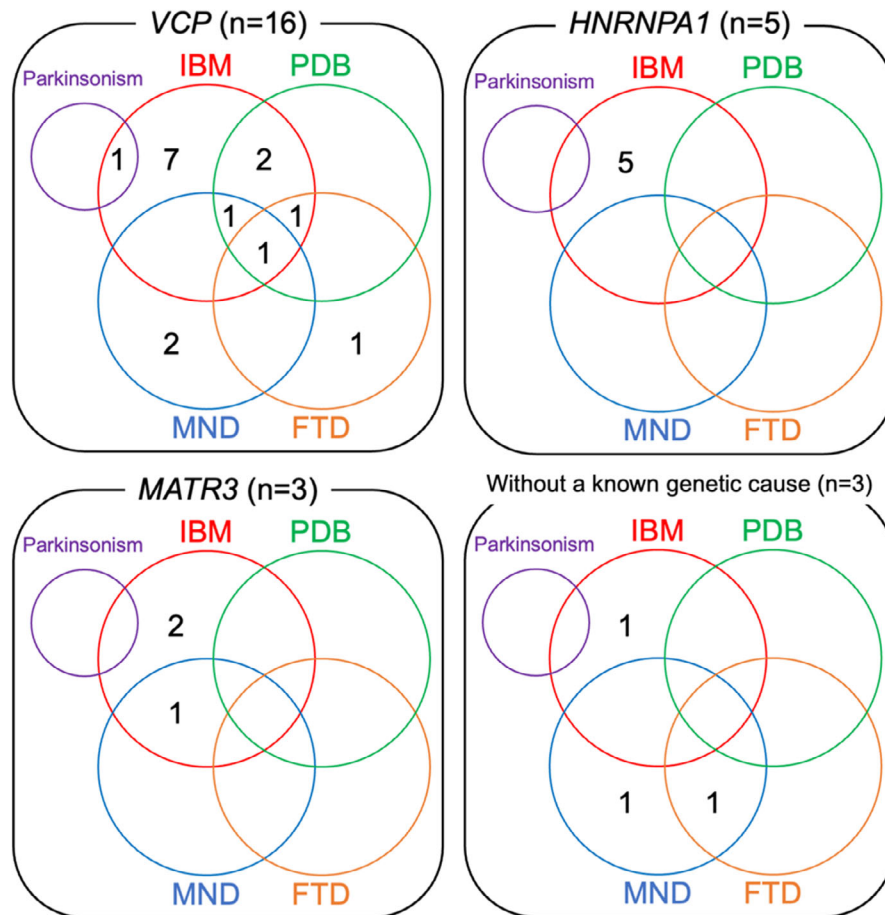
patients with *HNRNPA1* or *MATR3* mutations had PDB (Fig. 2). Three (60%) patients had lesions on the pelvic bones, 1 (20%) patient on the spinal vertebrae, and 1 (20%) patient on the femur. The onset of IBM or ALS preceded the onset of PDB in 3 cases, whereas IBM or ALS occurred after PDB in 2 cases. FTD was found in 4 out of 27 patients, with a mean age of onset of 50.8 years (range: 45–57 years). Behavioral disinhibition was present in 2 patients (50%), apathy or inertia in 2 (50%) patients, loss of sympathy or empathy in 2 (50%) patients, perseverative, stereotyped, or compulsive/ritualistic behavior in 2 (50%) patients, and executive dysfunction in 1 (25%) patient, but none exhibited hyperorality and dietary changes. As to the combination of the disease subtypes, 1 patient had IBM, ALS/MND, and PDB together, 1 patient had IBM and PDB together, 1 patient had ALS/MND together, and 1 patient had FTD alone. Parkinsonism occurred in 1 patient in the 60s. The patient was treated with levodopa and a dopamine agonist, which did not relieve the symptoms.

Abnormalities were frequently detected in creatine kinase test, needle electromyography, and muscle biopsy. Brain magnetic resonance imaging and perfusion single-photon emission computed tomography also frequently detected abnormal findings (Fig. 1J). Needle electromyography was performed on 21 patients, all of whom had abnormalities; 11 (52.4%) had acute denervation findings, 10 (47.6%) had chronic denervation findings, and 18 (85.7%) had myogenic changes. There were 13 cases (61.9%) with both denervation findings and myogenic changes. Muscle biopsy was performed on 20 patients (74.1%), and all of them had abnormal findings. The most frequent muscle histological finding was rimmed vacuoles (90.0%), followed by small angulated fibers (40.0%), small grouped atrophy (30.0%), and cytoplasmic inclusion bodies (30.0%), which suggested a combination of myogenic and neurogenic changes (Fig. 1K). However, most patients did not undergo bone-specific ALP test, bone x-ray, bone scintigraphy, bone biopsy, dopamine transporter scintigraphy, or metaiodobenzylguanidine myocardial scintigraphy to evaluate PDB or parkinsonism (Fig. 1J).

With regard to treatments, non-pharmacological therapies, such as rehabilitation, were provided for IBM. In some cases, artificial ventilatory management (tracheostomy positive pressure ventilation) was provided for respiratory failure, but the majority of patients had not received any treatments. The severity was assessed using classification of ALS in Japan. The results showed that 40.7% of the patients were “generally able to do housework and work (Stage I)” and 44.4% were “generally independent in daily living (Stage II)” at the diagnosis, which was relatively mild. At the last follow-up, 40.7%



**Figure 1.** (A) Histogram of age at onset of secondary survey participants. (B) Histogram of age at diagnosis of secondary survey participants. (C) Histogram of age at last follow-up of secondary survey participants. (D) MSP categories of secondary survey participants. (E) Familial history of secondary survey participants. (F) Genetic testing of secondary survey participants. (G) Initial symptoms of secondary survey participants. (H) Clinical symptoms of the entire course of the disease in secondary survey participants. (I) Severity classification assessed at diagnosis and last follow-up. (J) Laboratory findings in secondary survey participants. (K) Muscle biopsy findings in secondary survey participants.



**Figure 2.** Combination of clinical manifestations of the entire course of the disease in MSP subtypes. Numbers indicate number of patients.

were “requiring assistance in daily living (Stage III)” and 22.2% were “requiring tracheostomy and parenteral nutrition (tube feeding, central venous nutrition, etc.) and/or ventilator use (Stage V)” (Fig. 11).

We compared the clinical characteristics among cases with genetic variants in MSP-related genes. Age at examination, age at onset, and age at diagnosis were not significantly different among the groups (Table S7). The most common initial symptom was IBM in cases with variants in *VCP*, *HNRNPA1*, or *MATR3* gene. No bias was found toward IBM, MND, or FTD as initial symptoms in cases without known MSP-related gene mutations (Table S7). IBM developed most frequently during the entire course

of the disease in cases with variants in *VCP*, *HNRNPA1*, or *MATR3* gene (Fig. 2, Table S7). By contrast, MND was the most frequent symptom in cases without a known genetic cause.

## Discussion

At the 215th European Neuromuscular Center International Workshop on *VCP*-related Diseases Consortium, the nomenclature for MSP was proposed to be applied to cases with two or more of IBM, PDB, or ALS although ALS and FTD can be considered to be in the same disease spectrum.<sup>7,8</sup> Regarding diagnostic criteria for MSP, the

Cure VCP Disease clinical consortium recommended genetic testing if there is a family history of one or more phenotypes in an autosomal pattern.<sup>9</sup> Other study has proposed that one of the features of IBM and a genetic diagnosis of *VCP* mutation is sufficient to diagnose MSP1.<sup>10</sup> A recently published paper recommended radio-nuclide bone scan as PDB surveillance for individuals with confirmed pathogenic mutations in the *VCP* and/or MSP-related genes.<sup>9</sup> Although genetic testing is becoming widely accepted as a less invasive and more definitive diagnostic tool, MSP-related genetic testing is not covered by health insurance in Japan, and not all patients suspected of having MSP are necessarily tested. Therefore, this study used inclusion criteria that allowed the inclusion of patients with suspected MSP, although not genetically confirmed.

Myopathy is found in MSP types 1–6 and MSP-like disorders. It is probably the most frequent symptom, but its precise epidemiology is unclear.<sup>5,11</sup> Moreover, cases of pure IBM have been reported in most types of MSPs. Among MSPs, MSP1 is the most common, with rimmed vacuolar myopathy appearing most frequently, whereas non-VCP-MSPs frequently have distal dominant muscle weakness.<sup>11</sup> In our cases, cases with *VCP* and *HNRNPA1* mutations showed muscle weakness and atrophy mainly in the limb girdle and thigh muscles, and cases with *MATR3* mutation showed distal muscle weakness and atrophy in the lower and/or upper limbs. The two cases that showed cervical weakness had *VCP* or *MATR3* mutation, but none showed facial weakness. MSP5 with *MATR3* mutation is characterized by marked impairment of finger extensor muscle groups, nasal voice, hoarseness, difficulty swallowing, muscle pain after exertion, and respiratory dysfunction.<sup>12</sup> MSP1 with *VCP* mutation may have facial muscle involvement, such as ptosis, and respiratory dysfunction.<sup>13</sup> Cases with *VCP* mutation may present with muscle weakness in various regions and should be treated with caution.

ALS/MND was reported in all types of MSPs, but reportedly less so than in IBM and PDB.<sup>8</sup> In MSP1, the frequency of ALS/MND is approximately 9%, with numerous patients having both UMN and LMN signs, making it difficult to differentiate them from sporadic ALS based on clinical symptoms alone.<sup>14</sup> A review of 17 cases from 8 families diagnosed with IBMPFD reported that although UMN signs were evident in only 3 cases (18%), some motor neuron signs were identified in 11 cases (65%), and electrophysiologic testing often confirms the involvement of LMNs.<sup>15</sup> In our analysis, both UMN and LMN signs were clinically impaired in 4 of the 7 cases, UMN signs only in one case and LMN signs only in 2 cases, suggesting that a detailed combination of clinical and electrophysiological evaluation is important for ALS diagnosis in MSP.

FTD occurred in 30%, with a mean age of onset of 56 years, older than that in IBM (mean: 43 years) and PDB (mean: 42 years) in an analysis of 187 cases with MSP1, but relatively younger than FTD overall.<sup>14</sup> IBM, PDB, and FTD are observed in various combinations, but all three were present in 10% of cases. Among cases presenting with FTD, 16% were combined with IBM, 1% with PDB, and 3% with FTD alone.<sup>14</sup> In our analysis, 1 case had IBM, ALS/MND, and PDB combined, 1 had IBM and PDB combined, 1 had ALS/MND combined, and 1 had FTD alone. As in previous reports, the frequency of FTD alone was low, and the majority of cases were complicated by multiple symptoms.

PDB is a chronic focal bone disorder due to excessive bone resorption associated with inadequate remodeling, characterized by hypertrophy, sclerosis, kyphosis, and other morphological changes.<sup>16</sup> In an analysis of 17 patients with MSP from 8 families, 10 of the 17 patients developed PDB, and 8 of them had muscle weakness due to ALS or IBM. Of the 8 patients with PDB with muscle weakness, 3 had symptoms of muscle weakness before the onset of PDB and 5 had PDB before the development of muscle weakness.<sup>15</sup> A similar trend was also observed in 10 patients with *VCP* mutation and 4 patients with *HNRNPA2B1* mutation, indicating that the onset of PDB often preceded the onset of muscle weakness.<sup>15</sup> In our analysis, more cases of IBM or ALS developed before the onset of PDB than after the onset of PDB; thus, assessment of PDB complications is important in patients with MSP with muscle weakness. The low prevalence of PDB/FTD in our cohort may be due to the small sample size, the difficulty in diagnosing PDB/FTD, the fact that the prevalence was not classified by gene, and the bias in the survey methodology. Furthermore, because the survey was conducted among Japanese neurologists, patients with only the PDB phenotype were not included and that it was not known whether the surveyed neurologists referred IBM/ALS patients to specialists who could diagnose PDB.

Currently, parkinsonism has only been reported in MSP1, with a frequency of 4%. Parkinsonism with *VCP* mutation has typical clinical symptoms and responds well to medical therapy.<sup>14,17,18</sup> No pathogenic *VCP* mutation has been identified in the sporadic PD cohort, and *VCP* mutation is not a common causative gene for PD.<sup>19</sup> Our case did not respond to treatment with levodopa and dopamine agonists. Because the response to treatment varies from case to case, genetic testing is necessary when family history or comorbidities of MSP are confirmed.

This study has several limitations. First, the greatest limitation was the low frequency of responses (17.9%). Although informed consent was required for this study, the clinical study was conducted during the coronavirus disease 2019 pandemic, and patients with MSP were possibly

reluctant to see their physicians and had difficulty obtaining consent to participate in the study. Second, the inclusion criteria proposed in this study conflicted with the diagnostic criteria recommended in the Cure VCP Disease Clinical Consortium study, in which genetic testing is recommended as the golden standard for MSP diagnosis.<sup>9,10,20</sup> Under our study's inclusion criteria, patients may undergo expensive, inconclusive, and invasive testing. In addition, the inclusion criteria for FTD were limited to behavioral variant FTD. Semantic dementia was reported as a subtype of FTD in MSP in only a few cases.<sup>21</sup> Therefore, the inclusion criteria need improvement to identify patients with MSP with a more diverse phenotype based on genetic testing. Third, although this study was conducted with neurologists, orthopedic surgeons and psychiatrists should also be included to collect patients with only PDB or FTD phenotypes.

In conclusion, the low frequency of FTD and PDB may suggest that FTD and PDB may be widely underdiagnosed and undertreated in clinical practice. For the proper diagnosis of the disease, it is essential that the concept of the disease is widely recognized not only by neurologists but also by orthopedic surgeons and psychiatrists.

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Neuro-Muscular Center, National Hospital Organization Omuta National Hospital, Omuta, Japan; <sup>18</sup>Department of Neurology, National Hospital Organization Osaka Toneyama Medical Center, Toyonaka, Japan; <sup>19</sup>Department of Neurological Intractable Disease Research, Kagawa University Faculty of Medicine, Miki, Japan; <sup>20</sup>Department of Neurology, Kagawa Prefectural Central Hospital, Takamatsu, Japan; <sup>21</sup>Department of Neurology, Vories Memorial Hospital, Omi-hachiman, Japan; <sup>22</sup>Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Kita-ku, Okayama, Japan; <sup>23</sup>Department of Neurology, Brain Attack Center Ota Memorial Hospital, Fukuyama, Japan; <sup>24</sup>Department of Neurology, School of Medicine, Sapporo Medical University, Sapporo, Japan; <sup>25</sup>Department of Neurology, School of Medicine, Teikyo University, Itabashi-ku, Tokyo, Japan.

## Author contributions

SY, YT, JH, AM, RN, MK, RI, NS, HW, and MA conceived and designed the study. SY, YT, JH, AM, RN, MK, RI, NS, HW, MA, MMY, SM, TS, HT, MI, SK, AT, DT, NS, KT, MK, YT, KM, EN, TY, KS, AI, AM, and FS collected the clinical data. SY, YT, JH, AM, RN, MK, RI, NS, HW, and MA acquired and analyzed the data. SY, YT, JH, AM, RN, MK, RI, NS, HW, and MA drafted the manuscript and prepared the figures. All authors read and approved the final manuscript.

## Conflicts of interest

All the authors have stated explicitly that there are no conflicts of interest in connection with this article.

## Data availability statement

Anonymized data will be shared by request from any qualified investigator. Individual participant data will not be shared.

## References

1. Kimonis VE, Kovach MJ, Waggoner B, et al. Clinical and molecular studies in a unique family with autosomal dominant limb-girdle muscular dystrophy and Paget disease of bone. *Genet Med*. 2000;2:232-241.
2. Watts GD, Wymer J, Kovach MJ, et al. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nat Genet*. 2004;36:377-381.
3. Johnson JO, Mandrioli J, Benatar M, et al. Exome sequencing reveals VCP mutations as a cause of familial ALS. *Neuron*. 2010;68:857-864.

4. Kim HJ, Kim NC, Wang YD, et al. Mutations in prion-like domains in hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy and ALS. *Nature*. 2013;495:467-473.
5. Leoni TB, Gonzalez-Salazar C, Rezende TJR, et al. A novel multisystem proteinopathy caused by a missense ANXA11 variant. *Ann Neurol*. 2021;90:239-252.
6. Taylor JP. Multisystem proteinopathy: intersecting genetics in muscle, bone, and brain degeneration. *Neurology*. 2015;85:658-660.
7. Evangelista T, Weihl CC, Kimonis V, et al. 215th ENMC international workshop VCP-related multi-system proteinopathy (IBMPFD) 13-15 November 2015, Heemskerk, The Netherlands. *Neuromuscl Disord*. 2016;26:535-547.
8. Korb MK, Kimonis VE, Mozaffar T. Multisystem proteinopathy: where myopathy and motor neuron disease converge. *Muscle Nerve*. 2021;63:442-454.
9. Korb M, Peck A, Alfano LN, et al. Development of a standard of care for patients with valosin-containing protein associated multisystem proteinopathy. *Orphanet J Rare Dis*. 2022;17:23.
10. Roy B, Peck A, Evangelista T, et al. Provisional practice recommendation for the management of myopathy in VCP-associated multisystem proteinopathy. *Ann Clin Transl Neurol*. 2023;10:686-695.
11. Chompoonong P, Oskarsson B, Madigan NN, et al. Multisystem proteinopathies (MSPs) and MSP-like disorders: clinical-pathological-molecular spectrum. *Ann Clin Transl Neurol*. 2023;10:632-643.
12. Muller TJ, Kraya T, Stoltenburg-Didinger G, et al. Phenotype of matrin-3-related distal myopathy in 16 German patients. *Ann Neurol*. 2014;76:669-680.
13. Guo X, Zhao Z, Shen H, Qi B, Li N, Hu J. VCP myopathy: a family with unusual clinical manifestations. *Muscle Nerve*. 2019;59:365-369.
14. Al-Obeidi E, Al-Tahan S, Surampalli A, et al. Genotype-phenotype study in patients with valosin-containing protein mutations associated with multisystem proteinopathy. *Clin Genet*. 2018;93:119-125.
15. Benatar M, Wu J, Fernandez C, et al. Motor neuron involvement in multisystem proteinopathy: implications for ALS. *Neurology*. 2013;80:1874-1880.
16. Hashimoto J, Ohno I, Nakatsuka K, et al. Prevalence and clinical features of Paget's disease of bone in Japan. *J Bone Miner Metab*. 2006;24:186-190.
17. Regensburger M, Turk M, Pagenstecher A, et al. VCP-related multisystem proteinopathy presenting as early-onset Parkinson disease. *Neurology*. 2017;89:746-748.
18. Chan N, Le C, Shieh P, et al. Valosin-containing protein mutation and Parkinson's disease. *Parkinsonism Relat Disord*. 2012;18:107-109.
19. Majounie E, Traynor BJ, Chio A, et al. Mutational analysis of the VCP gene in Parkinson's disease. *Neurobiol Aging*. 2012;33:209.e1-2.
20. Pfeffer G, Lee G, Pontifex CS, et al. Multisystem Proteinopathy due to VCP mutations: a review of clinical heterogeneity and genetic diagnosis. *Genes (Basel)*. 2022;13:963.
21. Kim EJ, Park YE, Kim DS, et al. Inclusion body myopathy with Paget disease of bone and frontotemporal dementia linked to VCP p.Arg155Cys in a Korean family. *Arch Neurol*. 2011;68:787-796.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Inclusion criteria of behavioral variant frontotemporal dementia (FTD) of multisystem proteinopathy (MSP).

**Table S2.** Inclusion criteria of motor neuron disease (MND) of multisystem proteinopathy (MSP).

**Table S3.** Inclusion criteria of inclusion body myopathy (IBM) of multisystem proteinopathy (MSP).

**Table S4.** Inclusion criteria of Paget's disease of bone (PDB) of multisystem proteinopathy (MSP).

**Table S5.** Confirmation of genetic variants in multisystem proteinopathy (MSP)-related genes.

**Table S6.** Categories of multisystem proteinopathy (MSP).

**Table S7.** Comparison of clinical characteristics among cases with genetic variants.

**Table S8.** Genetic variants detected in each group of multisystem proteinopathy (MSP).