ALS1: Cu/Zn superoxide dismutase 1, soluble (SOD1)

In 1991, Siddique et al. [1] showed the linkage of FALS to chromosome 21q by positional cloning and demonstrated genetic locus heterogeneity in FALS. Rosen et al. [2] then reported a genetic linkage between FALS and a gene encoding cytosolic Cu/Zn superoxide dismutase (SOD1)—a homodimeric metalloenzyme that catalyzes the reaction of toxic superoxide anion O_2^- to O_2 and H_2O_2. Since SOD1 missense mutations were established as the first causative genes for ALS, the number of known mutations has increased to more than 185 so far (Additional file 1: Table S1). Most cases were inherited in an autosomal dominant manner, but the D90A mutation transmitted the disease in both an autosomal dominant and autosomal recessive manner. Globally, the most frequent SOD1 gene mutation is D90A. However, in the USA, the most frequent mutation was A4V, and in the UK and Japan, the most common mutations were I113T, and H46R, respectively. However, to our knowledge, no SOD1 mutation was reported from Ireland. Regarding clinical features of ALS with the SOD1 mutation, lower limb-onset and predominant LMN involvement are relatively common (Table 1). The D90A-homozygous mutation is associated with slowly progressive paresis in the legs that gradually spreads up to the arms, thoracic and bulbar musculature, with atypical non-motor features such as ataxia, neuralgic, aching pain, heat sensations, and bladder disturbance. Interestingly, it has been reported that patients with SOD1-related FALS greatly differed with respect to the age of onset of weakness, while the duration of the disease appears to be characteristic for each type of mutation. Some SOD1 mutants (D90A-homozygous, E100K, E100G, A89V, L84F, L84V, D76V, H46R, G37R, and G10V) tend to show a uniform phenotype, while other mutants (A4V, C6G, G41S, N86S, D90A-heterozygous, I112M, I113T, L144F, and V148I) have greatly variable phenotypes. The A4V, H43R, L84V, G85R, N86S, and G93A mutations have been associated with rapid disease progression and survival times shorter than 3 years, whereas the cases with G93C, D90A, or H46R mutations exhibit longer life expectancies, up to more than 10 years after disease onset [3–5]. These findings suggest that each type of SOD1 mutation may be associated with a different degree of toxicity. We examined two unrelated FALS families with H46R mutations (Fig. 1). The patients showed a uniform phenotype: the initial symptom was unilateral weakness of the flexor muscles in the distal lower limbs (Fig. 1) [6]. This might be attributed to mitochondrial respiratory chain dysfunction due to mutant SOD1 expression in the muscles as previously reported [7].

ALS2: Alsin

To date, more than 50 patients with mutations in the Alsin gene have been reported with early onset of the disease (~1 year). These patients generally belong to Middle Eastern, European, and Mediterranean countries, Japan, and China (Additional file 1: Table S1). All patients with ALS2 had homozygous or compound heterozygous mutations in the Alsin gene. Mutations in the Alsin gene cause three distinct disorders: infantile ascending hereditary spastic paraplegia (IAHSP), juvenile primary lateral sclerosis (JPLS), and autosomal recessive juvenile amyotrophic lateral sclerosis (JALS) (Table 1) [8, 9]. A recent study reported patients with ALS2 with nonsense and frameshift mutations in the Alsin gene who presented with generalized dystonia and cerebellar signs [10]. Although the phenotype-genotype correlation remains undetermined so far, most of the mutations predict truncated proteins, which could be unstable in structure and lose their function.

ALS4: Senataxin (SETX)

Senataxin (SETX) was initially identified as a causative gene for severe early-onset ataxia with oculomotor apraxia (AOA2), which is the second most common recessive ataxia after Freidreich's ataxia [11]. Later, heterozygous mutations were found in patients with the autosomal dominant form of juvenile-onset ALS [12]. ALS4 is characterized by slowly progressive distal muscle weakness and atrophy with pyramidal signs, sparing of bulbar and respiratory muscles, and frontal dysfunction (Table 1) [13]. So far, the T3I, L389S, T1118I, C1554G, K2018E, K2029E, R2136H, and I2547T mutations in the SETX gene have been identified in both patients with FALS and those with SALS with widely differing symptoms (Additional file 1: Table S1). In a recent report, a patient with late onset ALS4, bulbar involvement, and predominantly proximal distribution of amyotrophy presented with choreic movements and elevated alpha-fetoprotein levels [14]. In contrast, one study demonstrated that previously published ALS4-related missense mutations are most likely to be non-pathogenic and just polymorphisms [15]. Therefore, we should carefully interpret the significance of SETX missense mutations in the absence of functional assays.

ALS5: Spastic paraplegia 11, autosomal recessive (SPG11)

Mutations in the Spatacsin (SPG11) gene represent the most common form of autosomal recessive hereditary spastic paraplegia with thin corpus callosum (HSP-TCC) [16]. Recently, SPG11 mutations have been identified in patients with the autosomal recessive form of juvenile ALS, indicating a wide clinical spectrum for SPG11 mutations [17]. The SPG11 mutations can be associated with an intrafamilial phenotypic heterogeneity, including atypical ALS and classic HSP-TCC [18]. To our knowledge, at least 28 patients with ALS5 have been described with juvenile onset of the disease, ranging

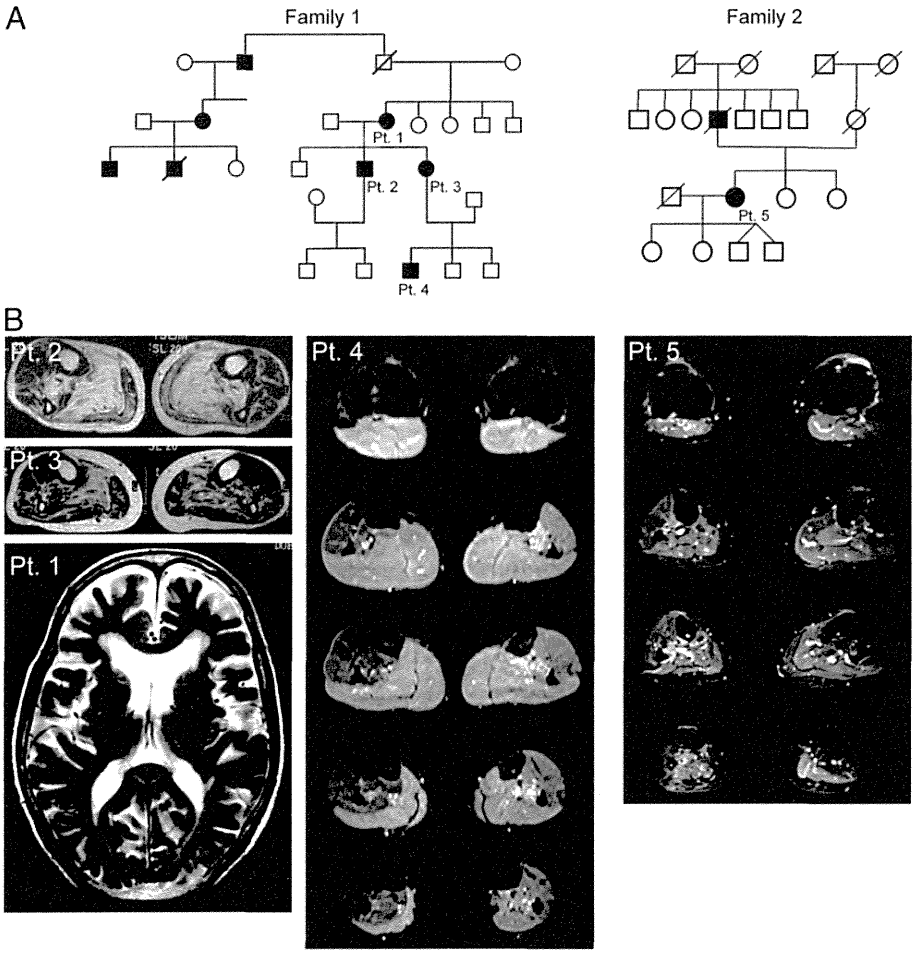

Fig. 1 Two FALS families with the SOD1 H46R mutations. **a** Family trees of Family 1 and 2. All of the patients showed the same uniform feature that initial symptoms were restricted to the flexor muscle group in the unilateral distal leg. **b** Short-T1 inversion recovery MR images revealed high intensity lesions in the gastrocnemial and soleus muscles of the patient 2, 3, 4, and 5. Brain MRI of patient 1 showed frontal lobe-dominant atrophy

from 7 to 23 years (Table 1 and Additional file 1: Table S1). All patients with ALS5 were associated with slow progression of symptoms with apparent UMN involvement (Table 1). It has been reported that the absence of thin corpus callosum, white matter alterations, cognitive deficits or mental problems clearly differentiates ALS5 from HSP-TCC [17]. At this point, it is unclear why the SPG11 mutations lead to clinical phenotypes resembling ALS or HSP-TCC.

ALS6: Fused in sarcoma/translocated in liposarcoma (FUS/TLS)

Two independent studies have reported that mutations in the fused in sarcoma/translocated in liposarcoma (FUS/TLS) gene were responsible for ~3 % of FALS and <1 % of SALS cases [19, 20]. FUS/TLS mutations, as well as TAR DNA-binding protein (TDP-43) mutations, have been increasingly reported from Asian countries [21, 22]. Some FUS/TLS gene mutations have been observed in patients with the juvenile form of ALS beginning at younger than 25 years [23–25, 22]. Case studies with the R521C mutation in the FUS/TLS gene emphasized the phenotypes of weakness of the neck and proximal muscles, which may be a clinical hallmark of ALS [26]. Most of the reported cases with the FUS/TLS mutation had no cognitive change. However, some of the patients with juvenile ALS with truncating FUS/TLS mutations have had mental retardation [27, 22].

Most ALS-related FUS/TLS mutations are located at the highly conserved regions of exon 15 that include the non-canonical nuclear localization signal (PY-NLS). Recent studies have shown that the mutations that nullify the PY-NLS lead to redistribution of FUS/TLS to the cytoplasm, where it is recruited into stress granules [28–30]. Notably, the degree of cytosolic mislocalization has been shown to be inversely correlated with the

age of disease onset [29]. It has been reported that the truncating mutation R495X was associated with an aggressive disease course, whereas the K510R mutation showed a mild phenotype with disease duration ranging from 6 to 8 years [31].

ALS8: Vesicle-associated membrane protein-associated protein B (VAPB)

A mutation in the vesicle-associated membrane protein-associated protein B (VAPB) gene was initially reported in Brazilian families with motor neuron disease with a wide range of phenotypes: late-onset spinal muscular atrophy, atypical ALS, or typical ALS [32]. In addition, several patients showed autonomic abnormalities, including chronic intestinal constipation, and sexual dysfunction [33]. So far, the T46I, P56S, and V234I mutations in the VAPB gene have been described in patients from Brazil, Japan, the United Kingdom, and the Netherlands (Additional file 1: Table S1). Further investigation will be required to understand the phenotype-genotype correlation.

ALS9: Angiogenin (ANG)

A cohort study in Ireland has identified several mutations in the angiogenin (ANG) gene in patients with ALS of Irish and Scottish background, both in familial and sporadic cases [34]. Subsequent clinical studies confirmed the association of these mutations with ALS, and identified new mutations in people with backgrounds from Brazil, China, France, Germany, Italy, Netherlands, Sweden, and the USA (Supplementary Table 1). Frontotemporal dementia (FTD) was also reported in a large FALS pedigree with the K17I ANG mutation [35]. Moreover, a relationship between mutations in the ANG gene and Parkinson's disease has been revealed [36].

ALS10: TAR DNA-binding protein (TDP-43)

Several groups have identified mutations in a highly conserved region of TDP-43 in SALS and FALS cases [37–40]. Most mutations are located in exon 6, which encodes the conservative glycine-rich domain. The phenotype and genotype analysis study in patients with ALS having TDP-43 gene mutations revealed that they had earlier onset (53.4 years; range 28-78), predominantly upper limb onset (60.7 %), and longer disease duration (63.0 months; range 32.0-77.2), compared with those having SALS [41]. In Caucasians, 51.3 % of the patients had the upper limb onset, whereas 58.8 % of Asian patients had bulbar onset [41].

ALS11: FIG4 homolog, SAC1 lipid phosphatase domain containing (S. cerevisiae) (FIG4)

Mutations in the FIG4 gene are responsible for the recessive form of Charcot-Marie-Tooth disease (CMT4J), with early onset and involvement of both sensory and motor neurons [42]. Subsequently, the same group identified ALS as a rare manifestation of the gene [43]. The phenotype observed in patients with FIG4 mutations is still controversial. Some patients carried a diagnosis of definite or probable ALS, and other patients were diagnosed with PLS, associated with predominant UMN involvement. Personality changes were also reported in patients with ALS11.

ALS12: Optineurin (OPTN)

Maruyama et al. [44] identified mutations in the optineurin (OPTN) gene in 3.8 % of Japanese with FALS and 0.29 % of Japanese with SALS. Mutations in the OPTN gene were also detected in some patients with both FALS and SALS in cohorts of Italian, Danish, French, Turkish, and German patients (Additional file 1: Table S1). As mentioned later, the role of OPTN in the pathogenesis of ALS has been further examined in a recent publication on the TANK-binding kinase (TBK1) gene [45, 46]. The clinical phenotypes of OPTN-related ALS showed relatively slow progression and long duration before respiratory dysfunction, but the onset age of the eight individuals with mutations of OPTN ranged from 30 to 60 years [44]. Brain atrophy with personality change or depression was also observed in patients with ALS12.

ALS13: ataxin 2 (ATXN2)

Long polyglutamine tracts, including more than 34 CAG repeats in the ataxin 2 (ATXN2) gene, have been identified as a cause of spinocerebellar ataxia type 2 (SCA2) [47]. Recent studies revealed that intermediate-length polyglutamine repeats (between 24 and 33) within the ATXN2 gene can be a risk factor for patients with ALS in different ethnic groups [48–50]. However, whether the clinical features of patients with ALS can be affected by ATXN2 intermediate-length repeats is still controversial [49–51].

ALS14: Valosin-containing protein (VCP)

Using exome sequencing, Johnson et al. [52] identified a R191Q mutation in the valosin-containing protein (VCP) gene in an Italian family with autosomal dominantly inherited ALS. Screening of the VCP gene in a cohort of ALS cases identified several mutations including a pathologically proven case of ALS. Mutations in the VCP gene have previously been identified in families with inclusion body myopathy, Paget disease, and frontotemporal dementia (IBMPFD) [53]. The phenotype of patients with VCP mutations shows intrafamilial variations from IBMPFD to FALS [54]. This suggests that motor neuron disease is part of the clinical spectrum of multiple proteinopathy of VCP-associated disease.

ALS15: ubiquilin 2 (UBQLN2)

Recent studies have revealed that ubiquilin 2 (UBQLN2), which regulates the degradation of ubiquitinated proteins, plays a pathogenic role in the X-linked form of ALS with or without FTD [55]. In an original case, the disease was transmitted in a dominant fashion with reduced penetrance without male-to-male transmission of the disease. Age at onset was significantly different between male and female patients, with male patients having earlier age of onset [55]. Mutations in UBQLN2 are not a frequent cause of ALS in the Dutch, French-Canadian, French, Irish, Taiwanese, and Korean population (Additional file 1: Table S1).

ALS16: σNon-opioid receptor (SIGMAR1)

Homozygosity mapping followed by direct sequencing has revealed a mutation in the σNon-opioid receptor (SIGMAR1) gene in patients in a consanguineous family with the autosomal recessive form of juvenile ALS in Saudi Arabia [56]. Furthermore, variants in the 3′-untranslated region (UTR) of the SIGMAR1 gene were reported in patients with frontotemporal lobar degeneration (FTLD) or motor neuron disease with FTLD [57]. However, the same family with the 3′-UTR mutation of the SIGMAR1 gene also had an expansion of a noncoding GGGGCC hexanucleotide repeat in the chromosome 9 open reading frame 72 (C9ORF72) [58]. This indicates that coding and noncoding variants located in the 3'-UTR of the SIGMAR1 gene are not the cause of FTLD-MND.

ALS17: chromatin modifying protein 2B (CHMP2B)

Mutations in the charged multivesicular body protein 2B (CHMP2B) gene have been initially identified in patients with FTD [59]. Although the phenotype is predominantly FTD, ALS has been reported as a rare manifestation of the gene [60, 61]. Neuropathology of the patient with the mutation showed LMN predominant disease with ubiquitylated inclusions in motor neurons [60]. Thus, classical ALS and PMA without corticospinal findings are phenotypes associated with mutations in the CHMP2B gene.

ALS18: profilin 1 (PFN1)

Exome sequencing followed by direct sequencing has shown mutations in the profilin 1 (PFN1) gene, which is a central regulator of actin dynamics in some FALS cases [62]. However, cohort analyses of patients with FALS and those with SALS from France and Quebec, Italy, Germany, the Nordic countries, and the United States suggested that the PFN1 mutation is a rare cause of ALS (Additional file 1: Table S1). In the original report, all patients with ALS18 showed limb symptoms at a relatively younger onset [62].

ALS19: v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4 (ERBB4)

A whole-genome sequencing and parametric linkage analysis identified the mutation in the v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4 (ERBB4) gene in patients of a Japanese family with late-onset, autosomal-dominant ALS [63]. An extensive mutational analysis revealed the same mutation in a Canadian individual with familial ALS and a de novo mutation in a Japanese case [63]. As of this moment, the genotype-phenotype correlation has not been determined.

ALS20: heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1)

Exome sequencing revealed mutations in the heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) gene in patients presenting with ALS and/or multisystem proteinopathy (MSP). These mutations are associated with a rare and complex phenotype associating FTLD, Paget disease of bone, and inclusion body myopathy [64]. Because the clinical information is not fully available, the phenotype of patients with mutant hnRNPA1 is still unclear.

ALS21: matrin-3 (MATR3)

A recent study using exome sequencing revealed mutations in the matrin-3 (MATR3) gene in FALS and FTD cases [65]. Initially, the S85C mutation in the MATR3 gene was reported as the cause of autosomal dominant distal myopathy with vocal cord paralysis (VCPDM) in large multi-generational families [66]. The phenotype observed in some patients carrying MATR3 mutations is still controversial. However, the clinical phenotype might be markedly similar to that observed in patients with mutations in VCP, hnRNPA1, and HNRNPA2B1 as MSP. We examined 2 sisters with VCPDM and S85C mutations in the MATR3 gene (Fig. 2) [67]. Both patients showed no UMN symptoms clinically; however, they showed chronic denervation and renervation on electromyography and muscle biopsy, split hand syndrome, and decremental motor responses to repetitive nerve stimulation, suggesting the involvement of LMNs [67].

ALS-FTD1: chromosome 9 open reading frame 72 (C9ORF72)

Two independent studies have discovered an expansion of a noncoding GGGGCC hexanucleotide repeat in the C9ORF72 gene that is associated with disease in a large FTD/ALS kindred linked to chromosome 9p [68, 69]. Analysis of extended clinical series found the C9ORF72 repeat expansion to be the most common genetic abnormality in both familial FTD (11.7 %) and familial ALS (23.5 %) [68]. Another study reported that the C9ORF72 intronic expansion was present in 11 % of the cohort,

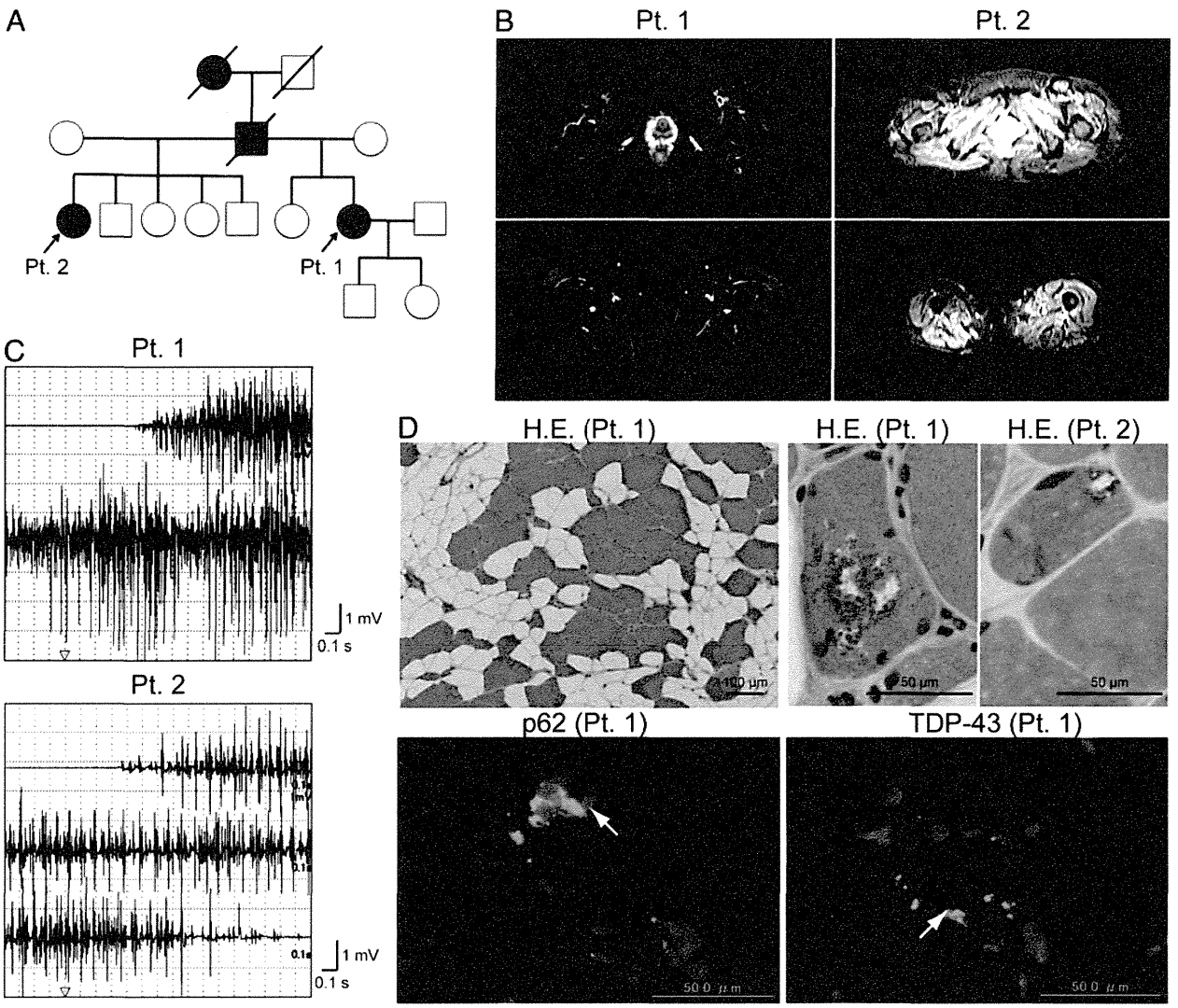

Fig. 2 A family with the MATR3 S85C mutation. **a** Family tree of cases with the MATR3 S85C mutation. The detailed clinical information was previously described [67]. **b** Short-T1 inversion recovery MR images revealed fatty and degenerative changes in the gluteus, quadriceps, and hamstring muscles of patient 1 and the paraspinal and gluteus muscles of patient 2. **c** Needle electromyography demonstrated chronic denervation in the vastus lateralis muscles of patients 1 and 2. **d** Muscle biopsy from patients 1 and 2 showed severe fatty and myopathic changes with rimmed vacuoles. Immunohistochemical analysis demonstrated p62- or TDP-43-positive sarcoplasmic granular staining in degenerating myofibers of patient 1. The observation of chronic denervation and renervation on electromyography and muscle biopsy, split hand syndrome, and decremental motor responses to repetitive nerve stimulation (data not shown) suggest the involvement of lower motor neurons in patients 1 and 2

43 % of FALS cases, and 7 % of SALS cases [69]. Therefore, C9ORF72 has been thought to be the most common cause of ALS in Caucasians, but rarer in other populations [70]. It is still controversial whether the patients with C9ORF72 expansion have shorter disease duration and relatively rapidly progression. C9ORF72 expansion can also cause parkinsonism and dementia. There is no association between the repeat length of the normal alleles, of the repeat in C9ORF72, and disease phenotype or age at onset in C9ORF72 mutation carriers or non carriers [71].

ALS-FTD2: Coiled-coil-helix-coiled-coil-helix domain containing 10 (CHCHD10)

Whole-exome sequencing identified a missense S59L mutation in the coiled-coil-helix-coiled-coil-helix domain containing 10 (CHCHD10) gene in a large family with a late-onset phenotype including motor neuron disease, cognitive decline resembling FTD, cerebellar ataxia and myopathy [72]. Multiple mitochondrial DNA deletions have been found in the skeletal muscles of patients with ALS-FTD2, suggesting mitochondrial DNA instability. Thus, the phenotype can vary according to affected organs.

TANK-binding kinase 1 (TBK1)

Recently, several studies using exome sequencing of moderate numbers of patients with ALS identified the TBK1 gene as an ALS gene, which is known to bind to and phosphorylate ALS-related proteins such as OPTN and p62 (SQSTM1/sequestosome) [45, 46]. Patients having ALS with the mutations frequently (~50 %) showed cognitive impairment [46]. Another study performing whole-genome sequencing in patients with FTLD-TDP found variants in the TBK1 gene, indicating a key role for the OPTN/TBK1 pathway in ALS and FTD [73].

Importance of genetic testing for ALS diagnosis

We describe the possible correlation between the genotype and phenotype, and aim to provide a clue to the diagnosis of ALS. ALS cases can be divided into 3 groups: juvenile onset less than 10 years or less 25 years, and adult onset type. Cases with juvenile onset were categorized into 2 groups because we could differentiate the genes that cause juvenile ALS alone from the genes that cause both juvenile and adult-onset ALS. ALS cases with juvenile onset less than 10 years include cases with mutations in the SPG11, Alsin, SETX, and SIGMAR1 genes (Fig. 3). When the symptoms are UMN-dominant, SPG and Alsin can be causative genes for ALS. In contrast, SETX might be responsible in cases with LMN-dominant symptoms such as PMA type. In ALS cases with onset from 10 to 24 years, SPG11, FUS, VAPB, SOD1, SETX, ATXN2, ANG, and UBQLN2 should be considered as a cause of ALS (Fig. 3). SPG or UBQLN2 might be a causative gene in UMN-dominant cases whereas FUS, VAPB, SOD1, and SETX should be examined in LMN-dominant cases.

In adult-onset ALS cases, many candidate genes should be excluded (Fig. 4). In patients who suffer from mental retardation, SPG11 may be responsible in UMN-dominant cases and FUS may be responsible in LMN-dominant cases. Coexistence with cerebellar ataxia may suggest the involvement of mutations of SOD1, ATXN2, Alsin, and SETX. Complications of motor neuropathy might occur in cases with mutations in the FIG4, SETX, VAPB, and SOD1 (homozygous D90A) genes. FTD can be present in cases with mutations in the UBQLN2, SIGMAR1, TDP-43, ANG, OPTN, CHMP2B, and C9ORF72 genes. Moreover, parkinsonism can be involved in cases with TDP-43, ANG, OPTN, and CHMP2B mutations. In some cases, muscle biopsy provides useful information for ALS diagnosis. Mitochondrial myopathy is reported in cases with CHCHD10 and SOD1 mutations (Fig. 1). FTD in combination with inclusion body myopathy and Paget's disease of bone in the patients or families strongly suggests mutations in the VCP, hnRNPA1, or MATR3 genes (Fig. 2).

Although these algorithms might provide some indications of what type of genetic abnormality might be present in a large enough family with somewhat consistent features, most families have a small number of affected individuals with wide variability. Thus, these algorithms may be ineffective. However, ethnic background plays a huge role in determining which genes are most likely. The proportion of ALS caused by a particular gene in a particular population can be a stronger predictor: C9ORF72 intronic expansion is very common in Caucasians, but rare in other populations. Therefore, the algorithms should be optimized based on ethnic backgrounds, and establishment of panels that examine all genes simultaneously would be ideal.

Another limitation is that phenotypes were described in limited number of patients in some genes except SOD1, FUS/TLS, TDP-43, and C9ORF72. This makes it is difficult to draw conclusive genotype-phenotype correlations. Moreover, some of the reported mutations were not necessarily pathogenic, just polymorphisms [15]. Thus, it is difficult to know which reported variants indeed cause the disease; it even more difficult in cases having oligogenic inheritance because their phenotype is derived from the combination of two genes.

Notably, half of the families with FALS do not have a mutation in the identified genes and therefore the genetic test is not necessarily informative for all cases of FALS. At this point, the determination that an individual has FALS is based on a family history rather than a genetic test. If one's family history is unknown or a parent passed away at a young age, testing is appropriate. Those patients with SALS without a family history can also be offered genetic testing. However, it is extremely important that this be done in the context of genetic counseling or after discussion with a neurologist about the implication of finding a mutation, as a mutation would mean that the ALS is hereditary. Although prenatal genetic testing technology exists, the patients and family members should discuss the procedure with their neurologist and genetic counselor for further information on this complex and personal matter [74].

Conclusions

There is no specific test or procedure to establish the diagnosis of ALS. A diagnosis of ALS can be established by ruling out other diseases that mimic ALS thorough comprehensive diagnostic examinations. Earlier diagnosis allows prompt initiation with a specific drug, such as riluzole, and accurate palliative care planning. The recent advances in the genetics of ALS have not only contributed to our understanding of the pathogenesis of ALS, but have also provided a tool for diagnostic procedures in some cases of ALS.

Despite all the progress achieved, the large majority of ALS genes remain unknown. The number of genes

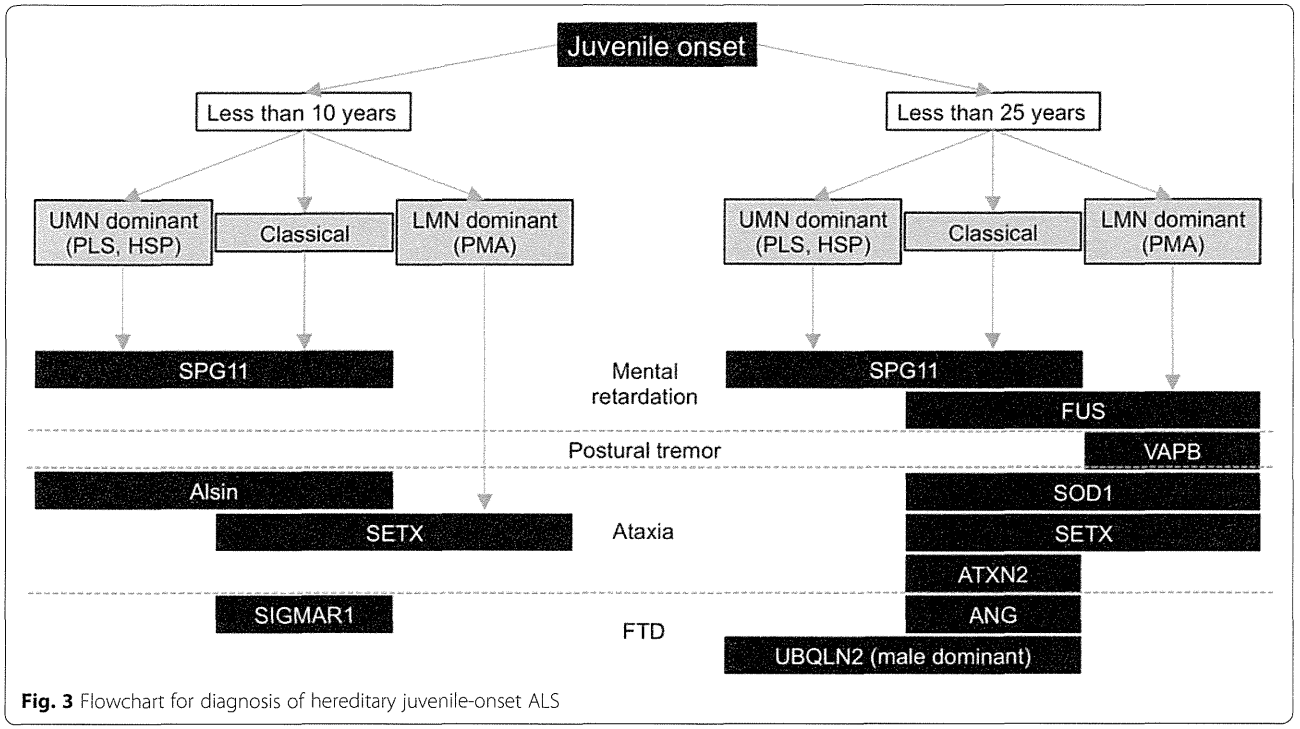

Fig. 3 Flowchart for diagnosis of hereditary juvenile-onset ALS

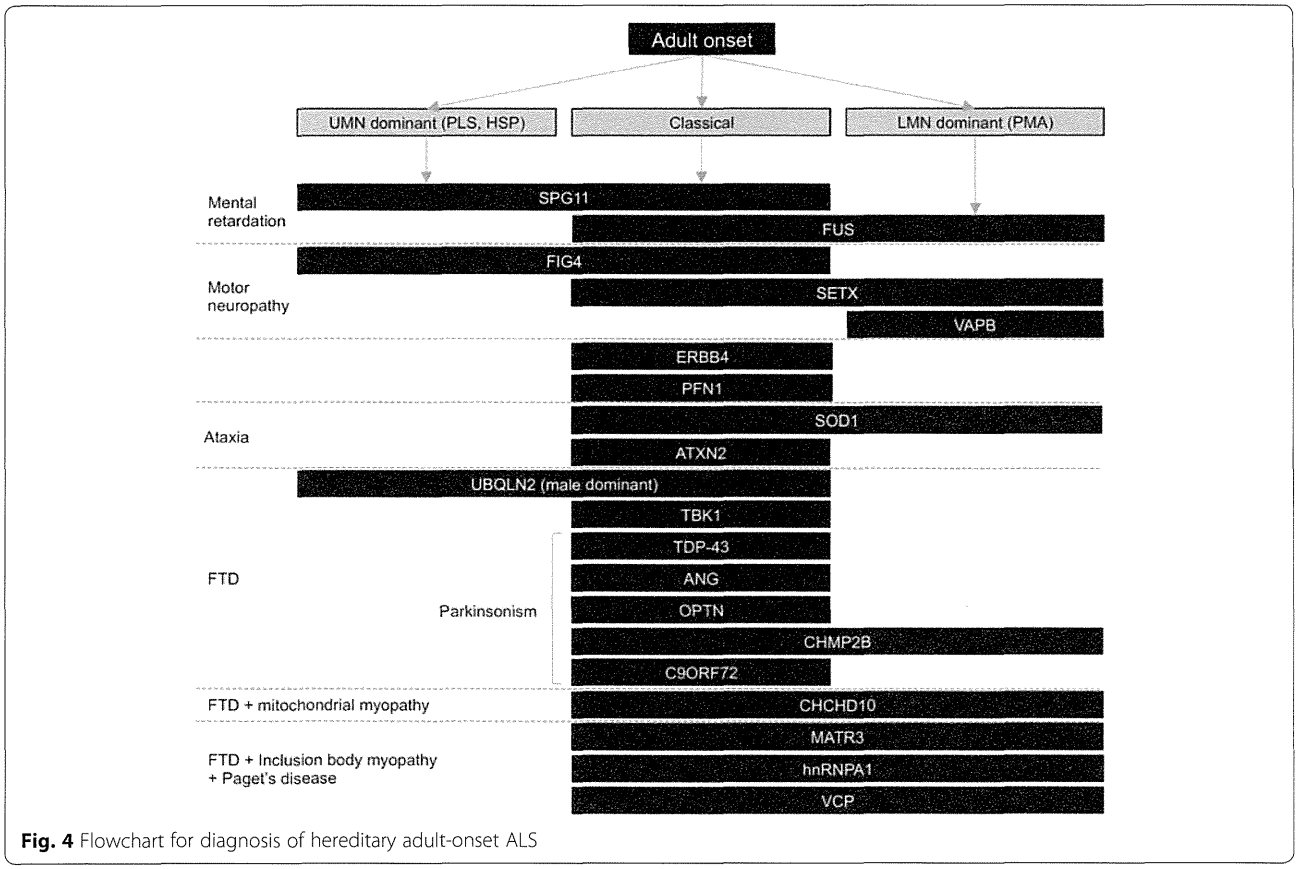

Fig. 4 Flowchart for diagnosis of hereditary adult-onset ALS

known to be involved in ALS is expected to continuously increase with the evolution of molecular genetics technology. Further discovery of the genetic factors in ALS will contribute considerably to the diagnosis, care, prevention, and treatment of ALS.

Additional file

Additional file 1: Table S1. The genotypes and phenotypes in previously-reported ALS cases with familial ALS-related mutations. UMN, upper motor neuron; LMN, lower motor neuron; UL, upper limb; LL, lower limb; FTD, frontotemporal dementia; N/A, not applicable; IAHSP, infantile ascending hereditary spastic paraplegia; JPLS, juvenile primary lateral sclerosis; JALS, juvenile amyotrophic lateral sclerosis; PMA, progressive muscular atrophy. (XLSX 96 kb)

Abbreviations

ALS: Amyotrophic lateral sclerosis; SALS: Sporadic ALS; FALS: Familial ALS; CNS: Central nervous system; SOD1: Cu/Zn superoxide dismutase; IAHSP: Infantile ascending hereditary spastic paraplegia; JPLS: Juvenile primary lateral sclerosis; JALS: Juvenile amyotrophic lateral sclerosis; SETX: Senataxin; SPG11: Spatacsin; HSP-TCC: Hereditary spastic paraplegia with thin corpus callosum; FUS/TLS: Fused in sarcoma/translocated in liposarcoma; PY-NLS: Non-canonical nuclear localization signal; VAPB: Vesicle-associated membrane protein-associated protein B; ANG: Angiogenin; FTD: Frontotemporal dementia; TDP-43: TAR DNA-binding protein; CMT4J: Charcot-Marie-Tooth disease; OPTN: Optineurin; ATXN2: Ataxin 2; VCP: Valosin-containing protein; IBMPFD: Inclusion body myopathy, Paget disease, and frontotemporal dementia; UBQLN2: Ubiquilin 2; SIGMAR1: σNon-opioid receptor; FTLD: Frontotemporal lobar degeneration; CHMP2B: Charged multivesicular body protein 2B; PFN1: Profilin 1; ERBB4: v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4; hnRNPA1: Heterogeneous nuclear ribonucleoprotein A1; MSP: Multisystem proteinopathy; MATR3: Matrin-3; VCPDM: Distal myopathy with vocal cord paralysis; C9ORF72: Chromosome 9 open reading frame 72; CHCHD10: Coiled-coil-helix-coiled-coil-helix domain containing 10; TBK1: TANK-binding kinase 1; LMN: Lower motor neuron; UMN: Upper motor neuron.

Competing interests

Both authors declare that they have no competing interests.

Authors' contributions

SY and YA drafted and revised the manuscript. Both authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Intramuscular dissociation of echogenicity in the triceps surae characterizes sporadic inclusion body myositis

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Background and purpose: Differential diagnosis of sporadic inclusion body myositis (s-IBM) and polymyositis (PM)/dermatomyositis (DM) is difficult and can affect proper disease management. Detection of heterogeneous muscular involvement in s-IBM by muscle sonography could be a unique diagnostic feature.

Methods: Sonography of the lower leg and forearm was performed in patients with s-IBM, PM/DM and control subjects (n = 11 each). Echo intensities (EIs) of the adjacent muscles [medial head of the gastrocnemius versus soleus and the flexor digitorum profundus (FDP) versus flexor carpi ulnaris (FCU)] were scored by three blinded raters. The mean EIs of these muscles were compared using computer-assisted histogram analysis.

Results: Both evaluation methods showed high echoic signals in the gastrocnemius of patients with s-IBM. EIs were significantly different between the gastrocnemius and soleus in patients with s-IBM, but not in those with DM/PM and the controls. In the forearm, although the EI of the FDP was higher in the s-IBM group than in the other groups, the EI differences between the FDP and FCU did not differ significantly between disease groups. The difference in area under the curves to differentiate between s-IBM and DM/PM was greatest between the gastrocnemius–soleus EIs (0.843; P = 0.006).

Conclusions: High echoic signals in the medial gastrocnemius compared with those of the soleus are suggestive of s-IBM over PM/DM.

Introduction

Sporadic inclusion body myositis (s-IBM) is a muscle disease that predominantly affects older individuals [1]. Diagnosis of typical s-IBM is straightforward with its characteristic preferential involvement of the deep finger flexors and knee extensors [2]. However, atypical presentations complicate its diagnosis and could lead to misdiagnosis as amyotrophic lateral sclerosis, polymyositis or muscular dystrophy [3,4]. Misdiagnosis can result in unnecessary therapies such as prolonged courses of steroids, as well as their adverse effects. Therefore, it would be useful to identify a measure to differentiate s-IBM from its mimics.

Muscular system imaging is useful for diagnosis and severity assessment of myopathic conditions [5]. Amongst modalities, magnetic resonance imaging (MRI) and sonography have been the most widely studied. Compared to muscle MRI, muscle sonography has the following advantages: (i) few contraindications and (ii) the ability to test patients at their bedside who are unable to be transported for MRI.

Recently, Noto *et al.* [6] observed heterogeneous involvement and reported dissociation of echoic signal intensities in patients with s-IBM, finding greater signal intensities in clinically more affected flexor digitorum profundus (FDP) than in less affected flexor carpi ulnaris (FCU). Cox *et al.* [7] assessed muscle MRI findings in patients with s-IBM and reported the

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degrees of fatty infiltration of each limb muscle. Intriguingly, the medial head of the gastrocnemius muscle had the most extensive fatty infiltration, whilst the soleus, another component of the triceps surae, was only moderately affected. This finding suggests that dissociation of the head of the triceps surae may be another diagnostic feature of s-IBM. However, detailed sonographic comparison of this muscle in s-IBM and other myopathies is lacking. Therefore, the aim of the present study was to compare the sonographic features of the triceps surae and forearm in patients with s-IBM and other inflammatory myopathies.

Methods

Subjects

Three groups were recruited and prospectively assessed: (i) patients with s-IBM who met clinico-pathologically defined IBM or clinically defined IBM criteria based on guidelines from the European Neuromuscular Center, with no family history of related conditions [2], (ii) patients diagnosed with either polymyositis (PM), dermatomyositis (DM) or myositis associated with a connective tissue disease according to established diagnostic criteria [8] and (iii) control subjects: asymptomatic persons with no neurological symptoms or signs. This study was approved by the Institutional Review Board of Vihara Hananosato Hospital and Tokushima University. The subjects provided written informed consent at the time of testing.

Sonography

A single technician (N.T.) blinded to patient diagnoses performed sonography using a LOGIQ7 (GE Healthcare, Tokyo, Japan) with a fixed 11-MHz linear-array transducer. The subjects were tested in the supine position and the right upper and lower limbs were studied. This unilateral assessment was chosen in order to avoid potential selection bias of highly correlated bilateral data from the same individual. Similarly, it was decided to study only on the right side to avoid potential side dependence of the sonographic parameters. By applying the transducer to the medial aspect of the mid-calf, the medial head of the gastrocnemius was identified where the soleus was visualized just under the gastrocnemius, with a clear margin by high-echoic fascicles (Fig. 1). Visualization of the FDP and FCU was performed as previously reported, by flexing the elbow and placing the probe 5 cm distal to the olecranon under a single view (Fig. S1) [6].

Visual assessment of muscle echo intensity (EI) was scored by three examiners who routinely performed muscle sonography but who were blinded to the diagnoses and scores of the other raters. Four muscles (the medial head of the gastrocnemius, soleus, FDP and FCU) were rated based on the modified Heckmatt rating scale as follows: (i) normal, (ii) slightly increased muscle EI with normal epimysium reflection, (iii) moderately increased muscle EI with reduced epimysium reflection and (iv) severely increased muscle EI with no clearly identifiable epimysium [9]. Because a bone may not be visualized in the lower leg, epimysium instead of bone was used as reference. The differences of the rating scales of the adjacent muscles (i.e. gastrocnemius versus soleus and FDP versus FCU) were calculated by comparing the scores of the respective muscles.

For quantitative assessment of EI, the mean pixel intensity of the muscle was measured by gray scale analysis using the standard histogram function in ImageJ, version 1.48 (National Institutes of Health, Bethesda, MD, USA). A region of interest (ROI) was set in a polygonal manner to include as much of the respective target muscle as possible without covering any bone or surrounding fascia. The EI value in the ROI ranged between 0 (black) and 255 (white). The mean EI of each muscle was obtained and averaged in each disease and control group. After standardizing the area under the histogram for each histogram, the grand-averaged histogram was obtained and the mean EI values were compared.

Data analysis

SPSS version 20.0J (Tokyo, Japan) was used for statistical analysis, using one-way ANOVA with Games–Howell *post hoc* test, receiver operating curves with the area under the curve, intraclass correlation coefficients (ICCs), Cronbach's alpha and Spearman's correlation coefficient where applicable. A P value of 0.05 was set as the threshold for statistical significance. A statistically significant P value was set at 0.05.

Results

Clinical characteristics

The subject characteristics are summarized in Table 1. Of 11 patients with s-IBM, six were classified as having clinico-pathologically defined IBM; the remaining five had clinically defined IBM. The patients in the PM/DM group had the following diagnoses and related conditions: PM, seven patients

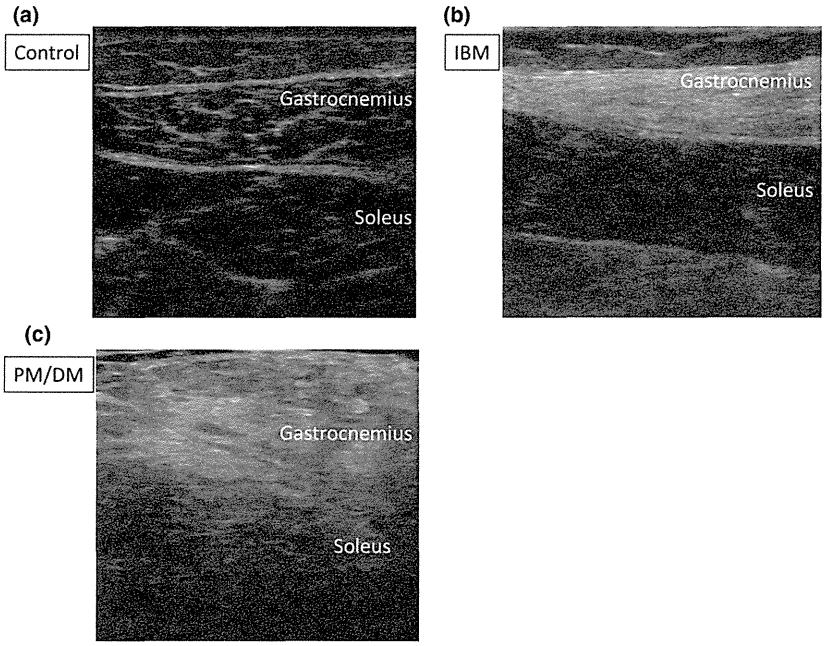

Figure 1 Representative sonographic axial images of the triceps surae. In the control subject (a), the echo intensities of the gastrocnemius and soleus muscle fibers are similarly low echoic with high-echoic perimysium. Gastrocnemius and soleus are clearly separated by high-echoic epimysium [Heckmatt rating scale (HS) = 1]. In the patient with inclusion body myositis (s-IBM) (b), there was significant contrast of hyperechoic gastrocnemius (HS = 3) and relatively normoechoic soleus (HS = 1). In the patient with polymyositis (PM/DM) (c), both muscles were hyperechoic and the separating epineurium was not clearly identifiable (HS = 4 each).

Table 1 Clinical characteristics of the subjects

	s-IBM (A)	PM/DM (B)	Control (C)	*P* value (ANOVA/*post hoc*)
Number	11	11	11	
Number of women	4	6	5	0.7 (ANOVA)
Age [mean ± SD; (range)]	74.5 ± 6.8 (62–82)	63.2 ± 12.4 (39–80)	73.5 ± 9.9 (57–88)	0.04 (A vs. B)
Duration of weakness in months [mean ± SD; (range)]	48.0 ± 40.2 (12–156)	17.5 ± 34.7 (1–120)	N/A	0.07 (A vs. B)
Serum CK [mean ± SD; (range)] (reference 40–200 U/l)	415.4 ± 268 (150–1053)	2037.3 ± 2531 (194–8003)	N/A	0.06 (A vs. B)

CK, creatine kinase; PM/DM, polymyositis/dermatomyositis; s-IBM, sporadic inclusion body myositis.

(three as definite PM and four as probable PM: three as an isolated condition and one each with scleroderma, rheumatoid arthritis, mixed connective tissue disease, primary biliary sclerosis); DM, four patients with definite DM. All patients with PM or DM responded to oral steroids; their scores on manual muscle testing of the bilateral biceps brachii or quadriceps improved at least 1° in the respective muscle by the modified Medical Research Council scale (4−, 4 and 4+). One patient with PM was positive for anti-signal recognition particle antibody. There was no significant difference in gender, but the mean age of the PM/DM group was less than in the s-IBM group ($P = 0.04$). Serum creatine kinase levels tended to be greater in the PM/DM subjects than in the s-IBM subjects ($P = 0.06$). The mean disease duration of the muscle weakness tended to be longer in patients with s-IBM than those with PM/DM ($P = 0.07$).

Sonography

Representative sonographic images are shown in Figs 1 and S1. In control subjects, the echoic signals were similar between the adjacent muscles, such as the gastrocnemius versus soleus and the FDP versus FCU. Patients with s-IBM showed selective hyperechogenicity in the gastrocnemius (Fig. 1b) and FDP (Fig. S1b), with relatively sparse EI in the neighboring soleus and FCU. In contrast, this selectivity was not evident in patients with PM/DM and these muscles tended to be equally hyperechoic; thus, the separating perimysium was not clearly identified (Figs 1c and S1c).

Table 2 summarizes the modified Heckmatt rating scale results in these muscles. In the controls, the muscles were rated as normal (score = 1) in most of the subjects, particularly in the forearm. However, patients with s-IBM and PM had higher scores. Patients with s-IBM had higher scores in the

Table 2 Subjective evaluation of echoic intensities by the modified Heckmatt rating scale. Averaged intensities of three raters (range of mean scores of each rater)

Group	s-IBM (n = 11) (A)	PM/DM (n = 11) (B)	Controls (n = 11) (C)	P values (one-way ANOVA with Games–Howell *post hoc*)
Gastrocnemius (GC)	3.12 (3.0:3.3)	1.91 (1.6:2.4)	1.12 (1.0:1.4)	***(A:B, A:C), **(B:C)
Soleus	1.97 (1.9:2.0)	1.91 (1.7:2.0)	1.09 (1.0:1.2)	**(A:C, B:C)
Difference GC:soleus	1.15 (1.0:1.3)	0.00 (−0.5:0.4)	0.03 (−0.2:0.3)	**(A:B, A:C)
Flexor digitorum profundus (FDP)	2.48 (2.2:2.7)	2.30 (2.1:2.5)	1.00 (1.0:1.0)	***(A:C), **(B:C)
Flexor carpi ulnaris (FCU)	1.63 (1.2:1.9)	1.69 (1.4:2.1)	1.00 (1.0:1.0)	***(A:C), **(B:C)
Difference FDP:FCU	0.85 (0.7:1.0)	0.61 (0.3:0.8)	0.00 (0.0:0.0)	***(A:C), *(B:C)

PM/DM, polymyositis/dermatomyositis; s-IBM, sporadic inclusion body myositis.
*<0.05; **<0.01; ***<0.001.

gastrocnemius than patients with PM ($P < 0.001$), but the scores in the soleus, FDP and FCU were similar amongst groups. This resulted in significantly greater scores for the difference between the gastrocnemius and the soleus in patients with s-IBM (i.e. selective hyperechogenicity in the gastrocnemius in these patients). This difference was not present between the FDP and FCU in the forearm. Table S1 shows the high reliability of measurements amongst the three raters [i.e. ICC(2, 1) > 0.7: Cronbach's alpha > 0.8] for the gastrocnemius and FDP, followed by the soleus, and the lowest reliability in the FCU. Differences between modified Heckmatt rating scale scores were compared between adjacent muscles. In the IBM group, 81.8% of patients had higher scores in the gastrocnemius than in the soleus, unlike the PM/DM and control groups ($P = 0.0002$: IBM versus PM/DM) (Table S2). In the forearm, the FDP had greater scores than the FCU in 54.5% of patients in the IBM group, but this frequency was not statistically significant compared to that of the PM/DM group ($P = 0.4$).

Histogram analysis

The averaged mean EIs are shown in Table 3 and Fig. 2. Similar to the modified Heckmatt score, the EIs tended to be significantly higher in the patient groups than in the control group. Of interest, the gastrocnemius in the s-IBM patients showed the greatest EI amongst all tested muscles, followed by the FDP in the same group. The difference in EIs between neighboring muscles (i.e. gastrocnemius versus soleus and FDP versus FCU) in the s-IBM group was significantly greater in the leg but not in the forearm. To compare the discriminatory power between s-IBM and PM, receiver operating curve analysis was performed (Table S3). The difference between the gastrocnemius and soleus that resulted in the greatest area under the curve (0.843, $P = 0.006$) combined with the best EI cut-off value (43.6) resulted in 72.7% sensitivity and 100% specificity (IBM versus PM/DM). Of note, the modified Heckmatt scales and mean gray scale values revealed significant positive correlations in all of the muscles (Fig. 3), suggesting high intra-test agreement. However, after excluding control group data, only the gastrocnemius and soleus showed significant correlations ($P < 0.001$). There was no correlation between (i) patient age, disease duration, patient strength by manual muscle testing or blood creatine kinase level and (ii) subjective finding (modified Heckmatt score) or gray scale, in any of the muscles in any of the groups.

Table 3 Echo-intensity analysis by histogram showing the averaged mean echo intensity

	s-IBM (A)	PM/DM (B)	Controls (C)	P values (one-way ANOVA with Games–Howell *post hoc*)
Gastrocnemius (GC)	103.2 ± 30.4	78.2 ± 18.1	51.0 ± 2.9	***(A:C), **(B:C), 0.08 (A:B)
Soleus	47.8 ± 24.5	60.0 ± 19.3	39.2 ± 3.4	*(B:C)
Difference GC:soleus	55.4 ± 38.0	18.2 ± 15.4	11.7 ± 14.3	**(A:C), *(A:B)
Flexor digitorum profundus (FDP)	86.1 ± 26.9	58.2 ± 21.1	38.7 ± 10.6	***(A:C), *(A:B, B:C)
Flexor carpi ulnaris (FCU)	66.5 ± 24.0	55.9 ± 28.9	38.7 ± 10.8	**(A:C)
Difference FDP:FCU	19.6 ± 22.0	2.2 ± 19.9	0.0 ± 8.5	*(A:C)

PM/DM, polymyositis/dermatomyositis; s-IBM, sporadic inclusion body myositis.
*<0.05; **<0.01; ***<0.001.

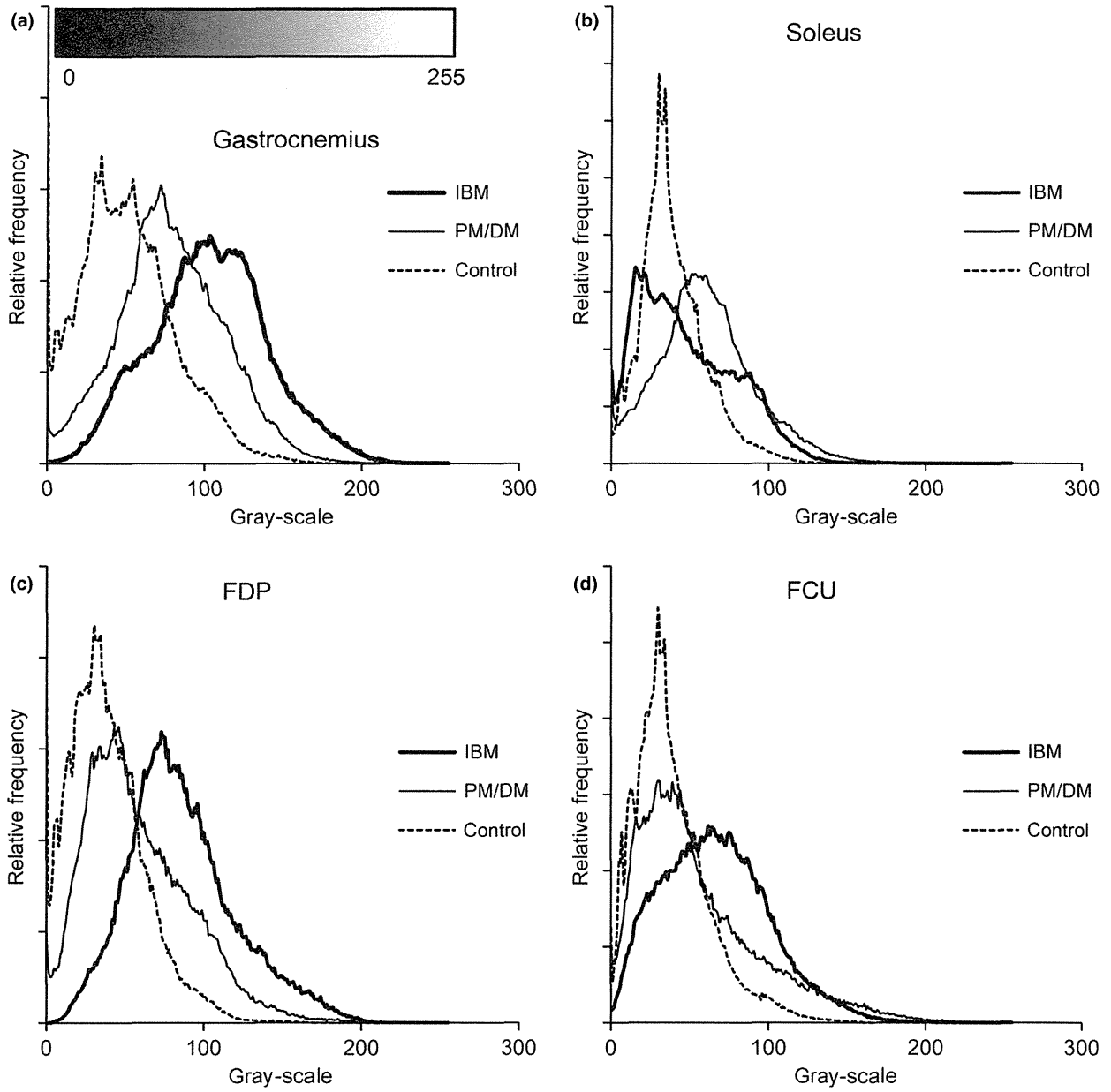

Figure 2 Averaged gray scale histograms of the sonographic images of four muscles in the three groups (n = 11 each). Pixel values range from 0 (black) to 255 (white) ((a) inset). Normal muscles have high peaks with narrow durations, reflecting homogeneous echo intensities. By contrast, the images of the myopathy patients tended to have higher (i.e. whiter) pixel values and broader durations than the control images, suggesting heterogeneous echo intensities.

Discussion

In this study, sonographic dissociation of EIs in the neighboring muscles in both the triceps surae and forearm muscles in patients with s-IBM was shown. This feature was more significant in the triceps surae and was able to discriminate s-IBM from DM/PM.

Sonographic–pathological association

Muscle sonography is considered a reliable and objective marker of muscle structure and underlying pathology in neuromuscular diseases [10]. Sonography has been reported to be correlated with clinical severity in diseases including spinal muscular atrophy, juvenile DM and muscular dystrophy, and to be correlated with

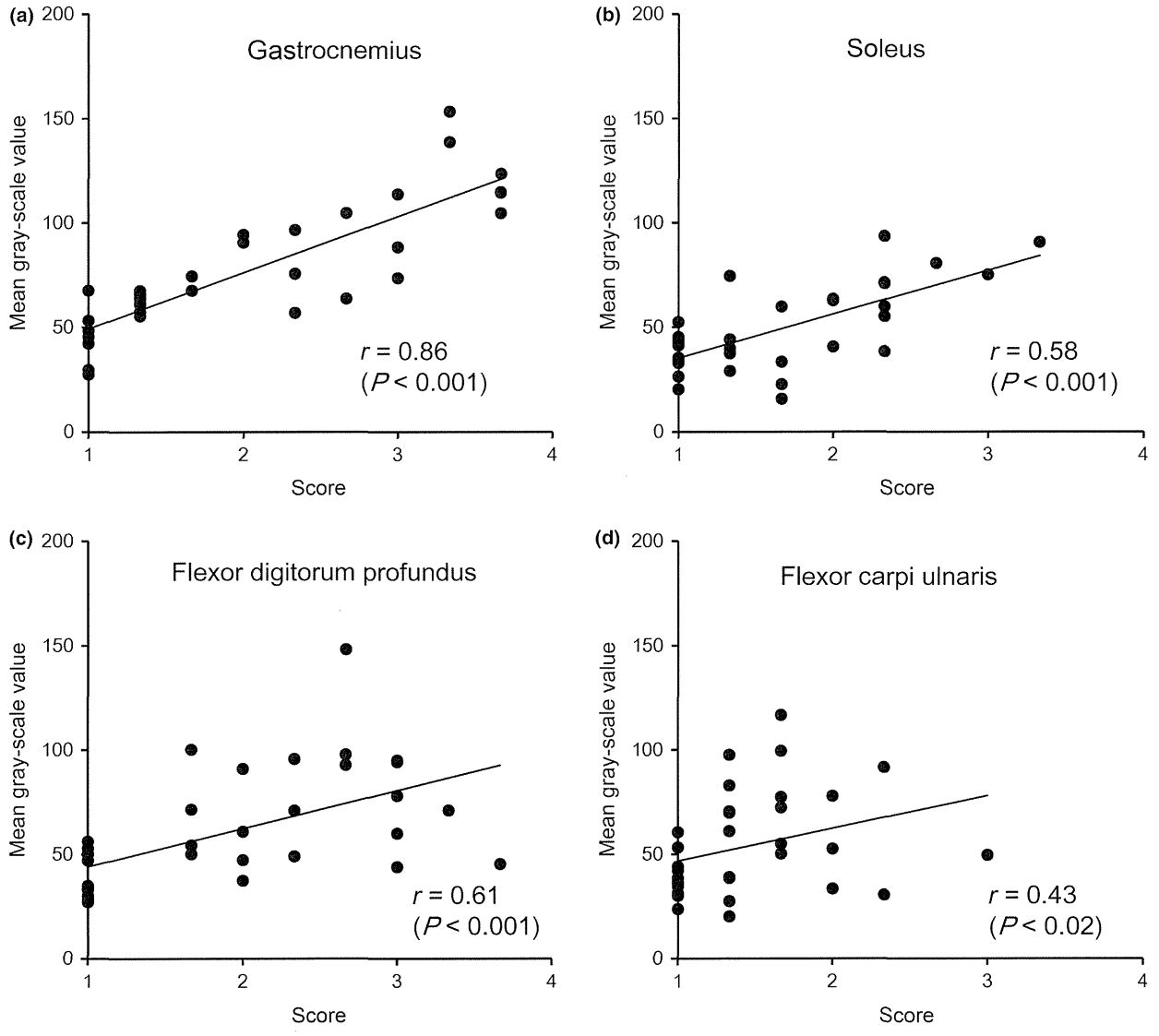

Figure 3 Correlations are shown between the modified Heckmatt scores (the averages of three raters) and the mean gray scale values in all the subjects (n = 33). Significant positive correlations were present in all the muscles suggesting reliability of the two evaluating methods. There were tendencies for stronger correlations in the triceps surae than in the forearm muscles.

findings of other diagnostic modalities such as MRI and muscle biopsy [11–14]. In many conditions, diseased muscles show abnormal echo signal intensity and size (e.g. thickness and volume). High EI indicates muscle atrophy, inflammation, fatty infiltration or fibrotic changes. Studies analyzing a canine model for muscular dystrophy and a single case report of amyotrophic lateral sclerosis showed that interstitial fibrous tissue most significantly affected EI; however, this observation has not been reported in myositis [15,16].

Heterogeneous muscular involvement in s-IBM

Selective and frequently asymmetric muscular involvement is a clinical hallmark of s-IBM, most notably in finger and wrist flexors and the quadriceps [17]. This clinical information has been confirmed by imaging modalities, such as MRI and sonography [6,7,18,19]. In contrast to the classic clinical description of s-IBM [17], extensive assessment of the upper and lower limbs and the pelvis by MRI has shown the highest frequency of fat-infiltrated muscles in the lower leg [7]. Amongst muscles in the lower leg, the medial head of the gastrocnemius had the highest frequency of severe fatty infiltration (approximately 85% of examined patients, the highest of the 42 upper and lower limb muscles), followed by the lateral head of the gastrocnemius (approximately 65%), both much greater than in the soleus (approximately 30%). This contrast was greater than the contrast between FDP (approximately

40%) and FCU (approximately 15%) [7]. The significantly different involvements between the medial head of the gastrocnemius and the soleus by MRI [7,18] and sonography in the present study might not be clinically obvious because examiners may have difficulty overcoming ankle plantar-flexor force, even with significant strength deficit by objective methods of assessment [20].

In contrast, MRI assessment of PM/DM showed similar frequencies of abnormal signal intensities by T2-weighted images between the medial head of the gastrocnemius and soleus [18], similar to the present data. Thus, all data consistently suggest that dissociating imaging features between these two muscles could differentiate s-IBM from PM/DM.

Our data showed similar degrees of sonographic abnormalities in the FCU and FDP in both disease groups. This is contradictory to the notion that PM/DM involves proximal muscles. Reimers *et al.* [21] studied 18 patients with DM by sonography and reported that the vastus lateralis, supinator and pronator teres muscles had the highest median EIs amongst the 16 muscles of the upper and lower limbs and trunk. Although they did not evaluate other forearm muscles, their data suggest the potential involvement of forearm muscles. Noto *et al.* [6] also reported similar sonographic abnormalities between s-IBM and PM/DM patients in the FCU, although the numbers were small (n = 6 each).

Study significance

Sporadic inclusion body myositis can be difficult to diagnose, and misdiagnosis is possible, especially in patients with atypical presentations [3,22,23]. Although identification of the characteristic pathological features by muscle biopsy is the diagnostic gold standard, its limited sensitivity may require multiple muscle biopsies to establish a diagnosis [24]. By contrast, a non-invasive imaging study could be utilized as a supportive diagnostic measure that can be tested repeatedly with little physical harm. From this standpoint, multiple imaging modalities could be used to determine if the predominant involvement is in the gastrocnemius rather than the soleus. As stated earlier, both MRI and sonography can fulfill this role. No study using computed tomography to compare densities between these muscles is known to us. Sonography has several advantages over MRI. Sonography generally involves lower cost for each session, it can be a useful alternative in patients for whom MRI scanning is contraindicated, such as those with pacemakers and other devices, and it can be performed at the bedside, and thus even claustrophobic patients can be assessed. Furthermore, the handiness of sonography enables testing where accessibility to MRI is limited (e.g. rural areas and for patients with limited mobility).

Muscle sonography has several potential technical difficulties that could affect EI determination. Because recording conditions such as thick subcutaneous fat can influence the absolute EI, comparison of multiple muscles under different views may not be reliable. In contrast, the method of comparing EIs of two muscles under a single view described in the current study is preferable due to its low variability. Interestingly, the visual scale and EI showed significant correlation in the triceps surae but not in the forearm muscles. This could be due to the smaller sizes of the forearm muscles compared to those of the calf, potentially leading to evaluation bias influenced by neighboring muscles in the forearm.

Another benefit of sonographic examination of patients suspected of having s-IBM or PM/DM is that the severity of myopathy in a particular muscle can also be assessed. Because a minimum degree of involvement is key for correct pathological diagnosis (e.g. false negative findings due to minimal sampling of involved muscle and a lack of useful information by sampling severely involved muscle tissue with fatty replacement), sonography-guided muscle biopsy is recommended.

Study limitations

This study has several limitations. First, the number of subjects was relatively small, and the overall sonographic characteristics of the muscles in patients with s-IBM are largely unknown. For example, it is not clear in our study if the sonographic contrast between the gastrocnemius and soleus is present in the early stages of IBM; there were only two patients with disease durations less than 12 months. Additional studies with larger numbers of subjects at different stages of disease could elucidate the natural course of sonographic findings in s-IBM. The significant dissociation between the FDP and FCU in s-IBM reported by Noto *et al.* was not reproducible in the present study. There are multiple explanations that could account for this difference [6]. First, their study had fewer subjects than ours (six patients in each group, compared with 11 in our study), potentially resulting in increased influence from individual subjects. Secondly, the mean Heckmatt rating scales in the PM/DM group were higher in the present study, suggesting that the patients with PM/DM in our study were more severely affected. Thirdly, the difference of Heckmatt scale scores between the FDP and FCU was used, whilst Noto

et al. used a relative ratio. Therefore, the ratio could change even when two muscles had identical differences [e.g. for FDP and FCU scales of 2 and 1 (case 1) and 4 and 3 (case 2), the difference between the scale scores is the same (1) but the ratio differs (2 vs. 1.33 for cases 1 and 2, respectively).

Secondly, it is unknown whether the dissociated appearance of the medial gastrocnemius and soleus is unique to s-IBM. For example, amyotrophic lateral sclerosis is commonly misdiagnosed as s-IBM clinically and ultrasonographically because of abnormally high echoic signals in the limb muscles [25,26]. Unlike s-IBM, however, the distribution is more diffuse in amyotrophic lateral sclerosis, such that sonography can probably also differentiate between these disorders. A large-scale sonographic evaluation including more diseases would clarify the significance of sonography for diagnosis of s-IBM and its mimics.

Thirdly, only the mean EI was used for quantitative analysis. It is possible that other histogram parameters and complex parameters such as texture analysis may also have diagnostic power for differentiation.

Conclusion

In conclusion, sonographic detection of the preferential involvement of the gastrocnemius over the soleus was present in patients with s-IBM; this characteristic could be more sensitive than the contrast between FDP and FCU and thus allow differentiation of s-IBM from PM/DM.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Representative sonographic axial images of the proximal forearm. In the control subject, the echo signals were similar between the flexor digitorum profundus (FDP) and flexor carpi ulnaris (FCU) [Heckmatt rating scale (HS) = 1 each]. In the patient with s-IBM, the FDP was hyperechoic (HS = 2), whereas FCU was spared (HS = 1). Such contrast was lacking in the patient with PM/DM (c), showing diffuse hyperechogenicity (HS = 3 each). FDS, flexor digitorum superficialis.

Table S1. Intraclass correlation coefficients [ICC(2, 1)] and Cronbach's alpha of subjective evaluating scales by three raters on all the subjects.

Table S2. Comparison of the modified Heckmatt rating scale (the average of the three raters). An averaged difference of the score <1 between adjacent muscles was considered as similar.

Table S3. Comparison of the area under the curve (AUC) by receiver operating curve (ROC) analysis between s-IBM and polymyositis/dermatomyositis using the averaged mean echogenicity by histogram analysis.

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