Title

Multisystem proteinopathy: Where myopathy and motor neuron disease converge

Journal

Muscle & Nerve, 63(4)

ISSN

0148-639X

Authors

Korb, Manisha K
Kimonis, Virginia E
Mozaffar, Tahseen

Publication Date

2021-04-01

DOI

10.1002/mus.27097

Received: 3 May 2020 | Revised: 8 October 2020 | Accepted: 18 October 2020

DOI: 10.1002/mus.27097

INVITED REVIEW

Answer questions and earn CME https://education.aanem.org/URL/JR81.

MUSCLE&NERVE WILEY

Multisystem proteinopathy: Where myopathy and motor neuron disease converge

Manisha K. Korb MD[1] | Virginia E. Kimonis MD[2] | Tahseen Mozaffar MD[1,3,4]

[1]Departments of Neurology, University of California Irvine, Orange, California

[2]Departments of Pediatrics, University of California Irvine, Orange, California

[3]Departments of Orthopedic Surgery, University of California Irvine, Orange, California

[4]Departments of Pathology & Laboratory Medicine, University of California Irvine, Orange, California

Correspondence
Tahseen Mozaffar, University of California Irvine, 200 South Manchester Ave, Suite 110, Orange, CA 92868.
Email: mozaffar@hs.uci.edu

Abstract

Multisystem proteinopathy (MSP) is a pleiotropic group of inherited disorders that cause neurodegeneration, myopathy, and bone disease, and share common pathophysiology. Originally referred to as inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD), attributed to mutations in the gene encoding valosin-containing protein (VCP), it has more recently been discovered that there are several other genes responsible for similar clinical and pathological phenotypes with muscle, brain, nerve, and bone involvement, in various combinations. These include heterogeneous nuclear ribonucleoprotein A2B1 and A1 (*hnRNPA2B1*, *hnRNPA1*), sequestosome 1 (*SQSTM1*), matrin 3 (*MATR3*), T-cell restricted intracellular antigen 1 (*TIA1*), and optineurin (*OPTN*), all of which share disruption of RNA stress granule function and autophagic degradation. This review will discuss each of the genes implicated in MSP, exploring the molecular pathogenesis, clinical features, current standards of care, and future directions for this diverse yet mechanistically linked spectrum of disorders.

KEYWORDS

amyotrophic lateral sclerosis, inclusion body myopathy, multiple system proteinopathy, Paget disease of bone, VCP

Abbreviations: AAA, ATPase Associated with diverse cellular Activities; ALP, alkaline phosphatase; ALS, amyotrophic lateral sclerosis; ApoE4, apolipoprotein E 4; ATPase, adenosine triphosphatase; BiPAP, bidirectional positive airway pressure; CK, creatinine kinase; CSF1, colony-stimulating factor 1; DMS-MFH, diaphyseal medullary stenosis with malignant fibrous histiocytoma; DNA, deoxyribonucleic acid; EMG, electromyography; ER, endoplasmic reticulum; FSHD, facioscapulohumeral muscular dystrophy; FTD, frontotemporal dementia; FUS, fused in sarcoma; GNE, UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase; hiPSCs, human induced pluripotent stem cells; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; hnRNPA2B1, heterogeneous nuclear ribonucleoprotein A2B1; IBM, inclusion body myopathy; IBMPFD, inclusion +body myopathy associated with Paget disease of bone and frontotemporal dementia; IκBα, NF-κB inhibitor alpha; LC3, microtubule-associated protein 1A light chain-3; LCD, low complexity domain; MATR3, matrin 3; MHC1, major histocompatibility complex 1; ML240, 2-(2-amino-1H-benzimidazol-1-yl) – 8-methoxy-N-(phenylmethyl) – 4-quinazolinamine; MND, motor neuron disease; MRI, magnetic resonance imaging; mRNA, messenger ribonucleic acid; MSP, multisystem proteinopathy; MTAP, methylthioadenosine phosphorylase; mTOR, mammalian target of rapamycin; Nbr1, neighbor of BRCA1 gene 1; NF-κB, nuclear factor kappa B; NMS-873, 3-[3-Cyclopentylsulfanyl-5-(4′-methanesulfonyl-2-methyl-biphenyl-4-yloxymethyl)-[1, 2, 4] triazol-4-yl]-pyridine; OPMD, oculopharyngeal muscular dystrophy; OPTN, optineurin; PDB, Paget disease of the bone; PolyPhen-2, Polymorphism Phenotyping v2; RANK, receptor activation of nuclear factor kappa B; RBP, RNA binding protein; RIN3, Rab and Ras Interactor 3; RNA, ribonucleic acid; RNP, ribonucleoprotein; SIFT, Sorting Intolerant from Tolerant; SQSTM1, sequestosome 1; TDP-43, TAR DNA binding protein; TIA1, T-cell restricted intracellular antigen 1; TM7SF4, transmembrane 7 superfamily member 4; TNFRSF11A, tumor necrosis factor receptor superfamily 11A; TNFRSF11B, tumor necrosis factor receptor superfamily 11B; UBA, ubiquitin associated; UPS, ubiquitin proteasome system; VCP, valosin-containing protein; VCPDM, vocal cord and pharyngeal weakness with distal myopathy.

The objectives of this activity are to: 1) understand and be able to use, in clinical evaluation, the phenotypic heterogeneity of this group of disorders; 2) understand, and be able to apply, in diagnostic evaluation, the genotypic heterogeneity of these disorders; 3) use knowledge about the genetic basis of these disorders to understand the current research and directions of future research.

1 | INTRODUCTION

Multisystem proteinopathy (MSP) comprises a group of rare genetic disorders that feature myopathy, bone disease, and neurodegeneration. These disorders are generally autosomal dominant and adult-onset, occurring as a result of various genetic defects to the autophagy pathway. Protein aggregates in muscle, brain, and bone, commonalities in pathophysiology, and the resultant clinical syndrome are what tie the different genetic syndromes together under the term MSP. The first ever recognized and most common disorder results from mutations in the valosin-containing protein gene (*VCP*), also termed MSP1.[1] Molecular analysis of patient families with similar clinical features but without a *VCP* mutation led to identification of mutations in the heterogeneous nuclear ribonucleoprotein A2B1 and A1 (*hnRNPA2B1* and *hnRNPA1*) genes, which have been termed MSP2 and MSP3, respectively.[2] Additional MSP mutations have been found in sequestosome 1 (*SQSTM1*; MSP4), matrin 3 (*MATR3*; MSP5), T-cell restricted intracellular antigen 1 (*TIA1*), and optineurin (*OPTN*), and the list will likely continue to grow.[3-7] MSP most commonly is associated with inclusion body myopathy (IBM), Paget disease of bone (PDB), frontotemporal dementia (FTD), and less frequently amyotrophic lateral sclerosis (ALS). The previously used term, inclusion body myopathy associated with PDB and frontotemporal dementia (IBMPFD), is no longer inclusive as several other phenotypes can be seen, including motor neuron disease, Parkinson disease, hereditary spastic paraplegia, and peripheral neuropathy, among others.[6,8] In 2013, the term multisystem proteinopathy (MSP) was proposed to group together the genetic diseases with phenotypical and pathological overlap to VCP disease and designated the three genes (*VCP*, *hnRNPA2B1*, and *hnRNPA1*) as MSP1-3.[9] Soon after SQSTM1 and MATR3 were added as MSP4[10,11] and MSP5.[11] In 2015, the VCP related diseases consortium met in The Netherlands for the 215th European Neuromuscular Centre International Workshop, and reinforced the MSP nomenclature.[12] It has also been suggested that the term be applied to cases that have two or more of IBM, PDB, or ALS, where ALS-FTD can be considered to be in the same spectrum of disease.[6]

Importantly, the various genetic syndromes of MSP share a common molecular pathogenesis stemming from dysfunction of the two major protein clearance pathways, the ubiquitin-proteosome system (UPS) and autophagy, which are also disrupted in ALS and inclusion body myopathy. VCP, hnRNPA2B1, hnRNPA1, SQSTM1, MATR3, and TIA1 all can be found in or interact with stress granules, which are cytoplasmic RNP granules that form due to cellular stress.[13] Meanwhile, VCP, SQSTM1, and OPTN mediate ubiquitin-dependent autophagy. On pathology, tissues involved in MSP have ubiquitin-positive inclusions that contain RNA-binding proteins (TAR DNA binding protein [TDP-43], hnRNPA1, hnRNPA2B1), and can also stain positive for proteins involved in ubiquitin-independent autophagy (p62/SQSTM1, VCP, OPTN, and ubiquilin-2).[14-16] It is evident that autophagy facilitates stress granule turnover, and impairment of this system can lead to neurodegeneration.[13]

1.1 | Myopathy

The myopathy in MSP is characterized by slowly progressive weakness and atrophy of skeletal muscles. There is typically proximal and distal weakness of upper and lower extremity muscles, foot drop, and scapular winging (Figure 1)[12]; paraspinal muscles are occasionally involved.[17] Myopathologically MSP1 is characterized by cytoplasmic rimmed vacuoles containing proteins such as tau, amyloid, and TDP-43.[14] Such rimmed vacuoles are also seen in other myopathies such as sporadic IBM. Inflammatory changes are rare, although upregulation of MHC-I or small inflammatory infiltrates have been observed.[12] Electromyography (EMG) and muscle biopsy frequently show mixed myopathic and neurogenic findings, suggesting the possible coexistence of a mild motor axonopathy.[18] While there are no described radiological hallmarks of MSP on muscle MRI, VCP patients commonly have involvement of both posterior and anterior compartments of the thighs and lower legs.[12] The creatinine kinase (CK) level is generally normal to mildly elevated.[19,20]

1.2 | PDB

PDB is a skeletal disease arising from dysregulation of osteoclast and osteoblast formation. VCP (like the other six genes in PDB) is associated with a predisposition to development of PDB due to its role in osteoclast differentiation and regulation, and it is also implicated (along with SQSTMI and OPTN) in autophagy.[21] The resultant disorganized and weak bone of PDB can result in bone pain, pathological fractures, hearing loss, and arthritis.[22] X-rays show coarse trabeculation, bone expansion, cortical thickening, and sclerotic lesions (Figure 2). Bone scintigraphy similarly shows anomalous concentration of radionuclides in these lesions. Serum testing can show elevated alkaline phosphatase (ALP) levels. While the most common symptom is bone pain, PDB patients may also be asymptomatic and found to have disease incidentally through imaging or lab testing.[21]

1.3 | FTD

Behavioral variant FTD, with changes in personality, behavior and executive function, is the more common subtype associated with MSP.[12] MSP-related FTD generally arises at a younger age of onset than isolated FTD.[23] Diagnosis is made with a brain scan showing the typical pattern of atrophy, and neuropsychologic testing. Brain histology is not specific or necessary for diagnosis, but shows gliosis, spongiosis, and neuronal intranuclear inclusions.[24]

1.4 | ALS

ALS in MSP is indistinguishable from sporadic or other familial ALS. Affected neuronal tissues in ALS and FTD have TDP-43 aggregates, similar to MSP-related myopathy.[14,25,26] Diagnosis is made clinically, supported by electrodiagnostic studies showing motor neuronopathy.

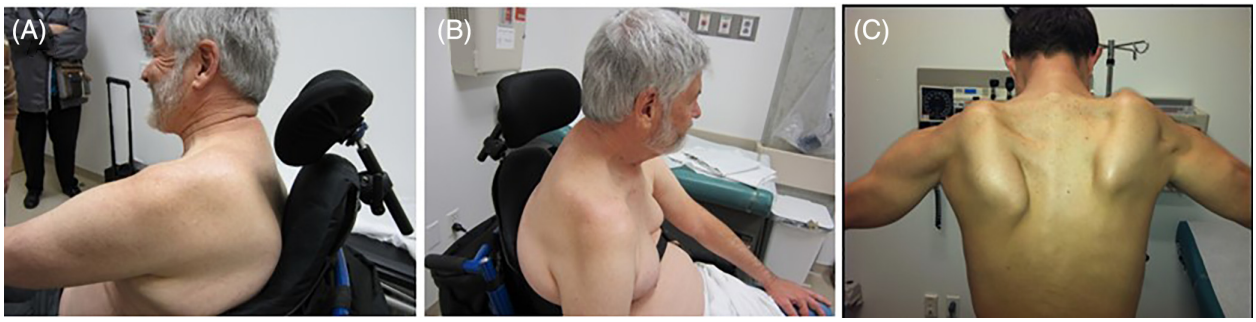

FIGURE 1 A,B, A 66 y-old man with VCP myopathy (R155H mutation) demonstrating upper extremity weakness and atrophy: A, Scapular winging and weakness of arm abduction. B, Deltoid, trapezius, pectoral, and forearm muscle atrophy. C, A 40 y-old man with VCP myopathy demonstrating marked bilateral scapular winging, worse on the left

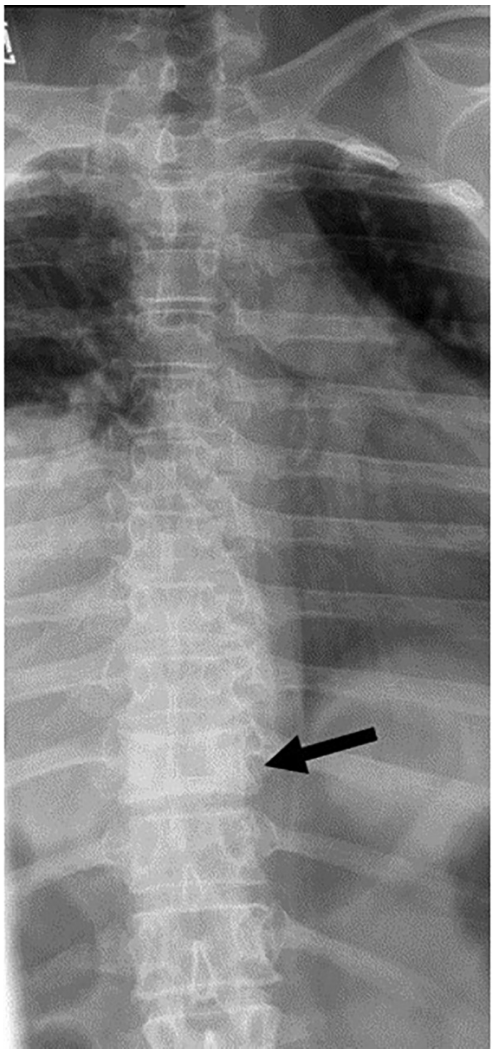

FIGURE 2 Skeletal X-ray of a 57 y-old woman with R155H associated myopathy and Paget disease reveals sclerotic changes and slight enlargement of the T10 vertebral body (arrow)

VCP mutations may account for ~1%–2% of familial ALS and VCP testing should be included in familial ALS workup.

1.5 | Testing for MSP mutations

There is vast phenotypic heterogeneity not only between and within the genetic syndromes, but also within members of the same family with an MSP disorder. To prevent misdiagnosis, genetic testing for mutations in MSP-related genes should be considered in patients with a family history of myopathy or motor neuron disease and/or dementia, even if individual family members are limited to one feature of MSP.[19] Similarly genetic testing should be considered in MSP mimics, including facioscapulohumeral muscular dystrophy (FSHD) with negative genetic testing for *FSHD1*, familial ALS, familial Paget disease, limb girdle muscular dystrophy, Welander myopathy, GNE myopathy, and myofibrillar myopathies. Patients who have an MSP mutation but only have myopathy should be periodically screened for the development of dementia and PDB, as these can occur later in the course of the disease. If clinical suspicion is high enough, with positive family history and/or at least two of the organ systems of MSP involved, it may be reasonable to forgo muscle biopsy and proceed straight to genetic testing when available.

1.6 | Management

Currently, there is limited treatment for MSP outside of supportive management.[12,23] Bisphosphonates have some efficacy in suppressing bone remodeling and ameliorating the bone pain of PDB, and early treatment may prevent pathological fractures and bone deformities.[19] However, there is limited literature on its effect in the PDB seen in MSP, and its effect in altering the natural history of the disease.

FTD lacks disease-modifying therapy. Lifestyle modifications that may be helpful for those with FTD and their families include implementing a daily routine, avoiding confrontation, participating in activities they enjoy, and removing triggers for maladaptive behaviors. Selective serotonin reuptake inhibitors may have some benefit for the behavioral symptoms of FTD, but again, there is limited literature regarding their efficacy in this condition.[12]

IBM and ALS are best managed with a multi-disciplinary team approach, including neurologists, physical and occupational therapists,

speech therapists, respiratory therapists, and social workers. Riluzole and edaravone are the only approved therapies for ALS, but their effect is not adequate to change the inexorable and lethal course of the disease. There is also still no effective treatment for slowing the progression of IBM.[12]

The clinical features, genetics, pathogenesis, and therapeutic strategies of multisystem proteinopathy syndromes will be discussed in this review article. We reviewed the literature on MSPs and expanded the current classification of MSP disorders (Table 1).

2 | MSP1: VCP

In 1966, McBride described PDB associated with muscle disease in a Scottish family, with an autosomal dominant pattern of inheritance,[27] and in 1982, Tucker described an inherited case of PDB with motor neuron disease.[28] Kimonis et al. described a family of 11 individuals in Illinois with early onset PDB associated with limb girdle muscular dystrophy in 2000.[29] Subsequently, Kimonis found a similar pattern in four other families who had inclusion body myopathy, PDB, and frontotemporal dementia, thus naming the syndrome IBMPFD.[30] Linkage analysis identified chromosome 9p13 as the implicated locus, and later missense mutations in the *VCP* gene, also called p97, were determined to be the pathogenic cause.[1,30] However, as early as 2002, additional genes were found to be responsible for the same syndrome, so genetic heterogeneity was established.[2,6,31] Overall, mutations in *VCP* are estimated to comprise about half of all MSP families[32]; thus, data on this gene comprise the bulk of our knowledge of MSP syndromes.

2.1 | Clinical features

Myopathy is the most frequent feature of *VCP*-related MSP, and occurs in about 90% of individuals.[19,33] The mean age of onset is 43 y,[19,33] and mean time to loss of ambulation is 13 ± 7 y.[12] The distribution almost always involves the proximal muscles, but with a high frequency of involvement of intrinsic hand muscles, foot drop, and scapular winging, and less frequently facial muscles. A study of 231 individuals with VCP mutations showed that PDB occurred in 42%, FTD occurred in 30%, ALS occurred in 9%, and Parkinson disease occurred in 4%.[33] Other less common phenotypes include cardiomyopathy, Charcot–Marie–Tooth disease, and anal incontinence, among others, although these do not occur in isolation and are found along with other clinical findings of the syndrome.[19,20,29,34-37] The PDB aspect of the disease has an average age of onset of 41 y, with a range of 23 to 65 y, and is not always symptomatic.[19,33] The PDB presents at a younger age in *VCP*-related cases than in typical cases. The FTD aspect has an average age of onset of 55 y and a range of 30 to 86 y,[19,33] which is also earlier than in non-*VCP* related cases. Life expectancy is reduced, with death at an average age of 58 y as a result of respiratory and cardiac failure.[19] Interestingly, although *VCP*-related MSP is often considered a triad of IBM, FTD, and PDB symptoms, only 10% of patients have symptoms of all three main conditions,[33] and the features can occur in various combinations in various orders of onset.

Within and between families with *VCP* mutations, there are immense variations and permutations of individuals' phenotypes, and specific mutations generally do not correlate well with the presentation. A notable exception is that individuals with an R159C mutation appear to have a later age of onset of myopathy and largely lack the bone disease component.[33] The R155H mutation, while common, does not have statistically significant differences in the age of onset of symptoms compared with other subtypes including R155C, R155P, L198W, and R159C.[33] Modifier genes have been studied and the apolipoprotein E 4 (ApoE4) allele has been associated with a higher incidence of dementia.[38]

VCP mutations have been observed in a diverse group of ethnic backgrounds, including mixed western European, Brazilian, African American, Hispanic/Apache, Israeli-Arab, Australian, Korean, Chinese,

TABLE 1 Clinical features of MSP mutations

MSP type	Gene	IBM/myo-pathy	MND	FTD	PDB	Other major associated phenotypes[a]
1	VCP	X	X	X	X	Parkinson disease, hereditary spastic paraplegia, Charcot–Marie–tooth disease type 2
2	hnRNPA2B1	X	X	X	X	Isolated PDB, fragile X-associated tremor ataxia syndrome
3	hnRNPA1	X	X	X	X	Isolated IBM
4	SQSTM1	X	X	X	X	Common in isolated PDB
5	MATR3	X	X	X	-	VCPDM
N/A	TIA1	X	X	X	-	Welander distal myopathy
N/A	OPTN	-	X	X	X	Autosomal dominant primary open angle glaucoma

Abbreviations: FTD, frontotemporal dementia; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; hnRNPA2B1, heterogeneous nuclear ribonucleoprotein A2B1; IBM, inclusion body myopathy; MATR3, matrin 3; MND, motor neuron disease; MSP, multisystem proteinopathy; N/A, not applicable.; OPTN, optineurin; PDB, Paget disease of the bone; SQSTM1, sequestosome 1; TIA1, T-cell restricted intracellular antigen 1; VCP, valosin-containing protein; VCPDM, vocal cord and pharyngeal weakness with distal myopathy.

[a]All of these mutations can also occur with isolated organ system involvement (ie, isolated myopathy without brain or bone involvement), and also can occur with various combinations of organ system involvement (ie, MND with FTD but without PDB).

and Japanese descent.[33,39-44] The incidence of the disease is reported to be 1/300000 to 1/600000 among Scottish and British patients, respectively.[37] However, the true incidence of the disease is likely higher, as patients with MSP1 may be asymptomatic well into adulthood or only be symptomatic from one of the organ systems affected. In addition, some family members may be asymptomatic carriers.[12] The discrepancy in calculating incidence arises from lack of awareness among physicians about the relatively newly described syndrome, vast phenotypic heterogeneity within and between families, and varying penetrance resulting in lack of all the components of the classic syndrome. Thus, comprehensive information about the incidence and prevalence, genotype–phenotype correlations, penetrance, and natural history of the disease is lacking. It will be important to raise awareness among healthcare professionals, ask appropriate questions about family history, screen for PDB and FTD for certain IBM or ALS patients, and consider genetic testing in those who have only parts of the triad.

2.2 | Histology and imaging

The main finding on histopathology is rimmed vacuoles, particularly in atrophic fibers (Figure 3A,B,E), without inflammation in the muscle (unlike sporadic IBM). The rimmed vacuoles contain protein aggregates of ubiquitin, TDP-43, and autophagy marker p62 (Figure 3G,H), as is seen in other rimmed vacuolar myopathies including sporadic IBM, GNE myopathy, Welander distal myopathy, and *MATR3* distal myopathy. Other pathologic attributes include increased fiber size variation, internalized nuclei, and abnormal accumulation of ubiquitylated proteins (Figure 3A,B,E). The muscle fibers infrequently show myofibrillar disorganization with larger accumulations of Z-disc or intermediate filament proteins like myotilin.[12] Neurogenic features, such as angular atrophic fibers, may also be seen (Figure 3B).[17] MHC-1 staining shows variable degrees of sarcolemmal and sarcoplasmic staining.

Muscle MRI in *VCP*-related myopathy tends to show involvement of nearly all muscles, with patchy regions of atrophied muscle replaced by fatty connective tissue. In the thighs and lower legs, both posterior and anterior compartment muscle involvement is common.[12] This pattern differs from several other muscular dystrophies that can tend to have highly selective patterns of muscle involvement.

2.3 | Pathophysiology

VCP is an ATPase involved in degradation and autophagy.[23] It is a highly conserved "ATPase Associated with diverse cellular Activities," classifying it in the AAA-ATPase superfamily.[23] It mediates ubiquitin-dependent cellular processes, including protein quality control, organelle biogenesis and elimination, membrane fusion, extracting ubiquinated proteins from multimeric complexes, and cellular signaling.[45] It also participates in DNA repair and regulation of autophagy, so disruption can interfere with cell death pathways.[46] There are currently over 50 mutations that have been reported in VCP, the vast majority being transmitted in an autosomal dominant and infrequently

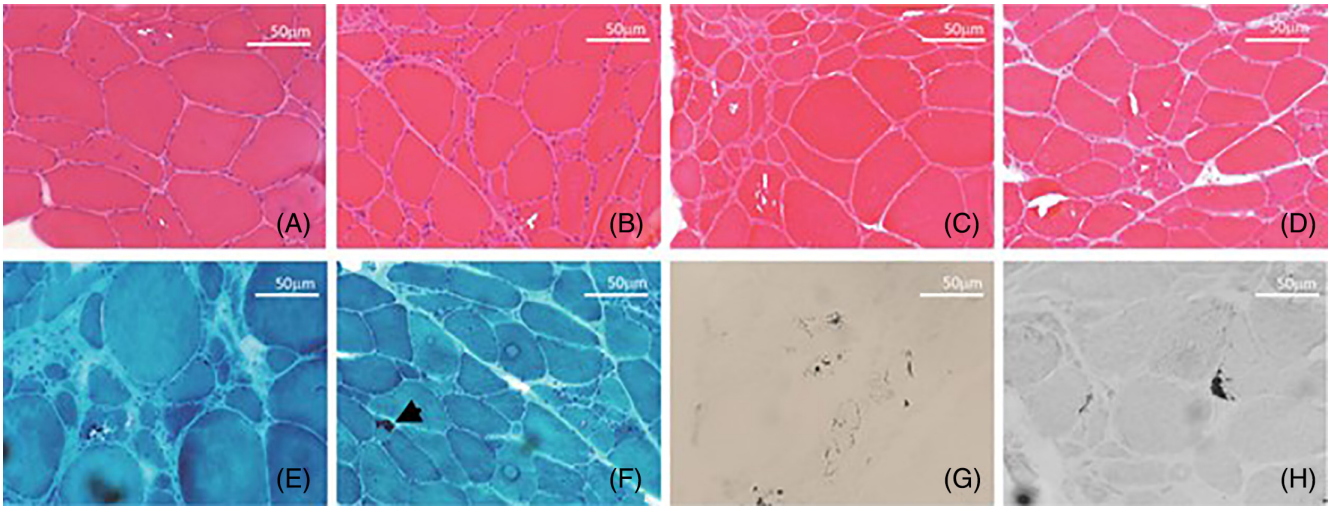

FIGURE 3 Myopathologic findings in MSP. A-D, Panels A-B show morphological changes on hematoxylin–eosin (H&E) stain from muscle biopsies from patients with VCP mutations (p.R155H and p.R191Q, respectively) while morphological changes are depicted in muscle biopsies from mutations in the hnRNPA1 (C) and hnRNPA2B1 (D). Abnormalities include rimmed vacuolar changes, marked fiber size variability, increased numbers of fibers with multiple internal nuclei, presence of small grouped atrophy, and increased endomysial connective tissue. B, The presence of "mixed" neurogenic and myopathic findings in these biopsies. E,F, Modified Gömöri-trichrome stain highlighting the rimmed vacuoles, multiple internal nuclei and increased connective tissue in muscle biopsies from a patient with p.R155H mutation in the VCP gene (E) and a patient with mutation in hnRNPA2B1 gene (F). Cytoplasmic bodies are also seen (arrowhead). G,H, Immunoperoxide staining for TDP-43 and p62 in a patient with p.R155H mutation in the VCP gene. There is diffuse expression of TDP-43 in these muscle fibers (G), particularly in areas of rimmed vacuoles. The rimmed vacuoles can also be stained for p62, highlighting a defect in autophagy in these muscles (H)

in a sporadic fashion.[12,17,47] Most are in the N terminus of VCP and are exonic missense mutations.[33]

VCP also helps defend against endogenous and exogenous cellular stressors, such as oxidative stress, temperature fluctuation, and mechanical stress.[46] Such factors can inhibit translation of mRNAs, provoking cells to produce transient cytoplasmic aggregates of ribonucleoprotein (RNP), called stress granules. VCP is required for autophagic degradation of these membrane-less organelles.[6,48] These are also seen in other MSP-related mutations, including RNA-binding proteins (hnRNPA2B1, hnRNPA1) and SQSTM1.[23] Furthermore, transfecting C2C12 mouse skeletal muscle cell line myoblasts with mutant VCP results in impaired stress granule resolution and clearance.[46] Consequently, there is considerable evidence that inability to degrade RNA granules by autophagy is a hallmark of VCP mutations, and the resultant protein aggregates can be observed in muscle, bone, and neuronal tissue.[49]

Missense mutations of the VCP gene are associated with toxic gain of function as indicated by studies of ATPase activity, with increased binding to its cofactors and reduced mitofusin levels; however, future studies will provide evidence for possible gain of function as a mechanism in the other MSPs.[50,51]

Given the autosomal dominant pattern of inheritance, the heterozygous state is pathogenic, although a homozygous mutation has recently been described in a man of Belgian descent who presented with younger age of onset and higher CK levels.[17] This finding supports the viability of homozygous VCP mutations, and that such patients can present with more severe phenotypes, similar to what can be seen in other protein aggregate myopathies, such as desminopathy and myotilinopathy.[52,53]

2.4 | Preclinical studies and future directions

Mouse and human VCP proteins differ by only one amino acid residue at position 684. Homozygous deletion of VCP resulted in early embryonic lethality in mice, while heterozygous mice with one wild-type allele and one deleted VCP allele were asymptomatic.[54] However, transgenic mice over-expressing a VCP mutation under a muscle-specific promoter had progressive weakness, and were found to have ubiquinated protein inclusions on muscle pathology.[55] Other VCP mouse models overexpressing the A232E allele under a ubiquitous promoter and the knock-in R155H mouse have shown progressive muscle weakness, cognitive abnormalities, and bone, spinal cord, and brain pathology with TDP-43 and ubiquitin positive inclusion bodies in myofibrils and brain tissue.[56-58]

A potential therapeutic target for VCP-related MSP would be inhibition of VCP ATPase activity, which could theoretically suppress the build-up of aggregated proteins or stress granules as seen in VCP MSP. Inhibition of VCP with NMS-873 and ML240 in a Drosophila model and patient fibroblasts corrected muscle damage and cell death.[59] Additionally, VCP disease-specific human induced pluripotent stem cells (hiPSCs) treated with autophagy stimulators rapamycin, perifosine, and AT101 showed a decrease in VCP pathology markers, including TDP-43, light chain 3 I/II, and p62/SQSTM1, showing that such stem cells could be a valuable tool for drug discovery.[60] A recent study used agonists of core autophagy proteins, ULK1 and 2, in mice to demonstrate increased stress granule disassembly through phosphorylation and activation of VCP.[61] Such regulation of stress granules holds promise for treating IBM and VCP-related myopathy. VCP mice have also been treated with arimoclomol, which prolongs activation of heat shock factor 1 in stressed cells, and demonstrated improved muscle strength and disease pathology.[62] Finally, Zhang et al. have shown that early inhibitors of VCP were able to rescue disease phenotypes of mitochondrial dysfunction and cellular death in a Drosophila model and in VCP patient fibroblasts.[59]

3 | MSP2 AND MSP3: HNRNPA2B1 AND HNRNPA1

Autosomal dominant missense mutations in the *hnRNPA2B1* and *hnRNPA1* genes were identified by combined linkage analysis and exome sequencing as another cause of MSP in families who had negative testing for *VCP*. In 2013 Kim et al. reported a family who had degeneration of muscle, bone, brain, and motor neurons who was clinically and histopathologically indistinguishable from VCP families, but had a mutation in *hnRNPA2B1*.[2] They also identified a family with myopathy and PDB, and another family with ALS, who had mutations in *hnRNPA1*.[2]

3.1 | Clinical features

The frequency of *hnRNPA2B1* and *hnRNPA1* mutations in MSP is estimated at <<1%.[2,32,63,64] Patients from each family identified by Kim et al. in 2013 had muscle biopsy findings of atrophic fibers, central nuclei, and rimmed vacuoles as seen in IBM (Figure 3C,D,F demonstrate similar findings in other patients). In normal muscle, hnRNPA2B1 and hnRNPA1 are located exclusively in nuclei, but in MSP patients the hnRNPA2B1 can accumulate as cytoplasmic inclusions in a minority of muscle fibers.[2]

Family 1 from Kim's study, with an hnRNPA2B1 mutation, had an autosomal dominant pattern of myopathy, PDB, dementia (diagnosed with FTD at autopsy in one of the family members), and motor neuron dysfunction, in various combinations.[2] Family 2 had a dominant pattern of myopathy and PDB, associated with a missense mutation in hnRNPA1. Finally, Family 3 exhibited a dominant pattern of ALS, which was linked to a missense mutation at the same residue of hnRNPA1.

A novel *hnRNPA1* variant was identified on whole exome sequencing in a Japanese population of ALS.[65] Additionally, a novel mutation in *hnRNPA2B1* was identified in a Chinese family with multiple members with early onset PDB, but no member had any of the other MSP features.[63] At this time, additional MSP2 and MSP3 families have not been identified, making the hnRNP syndromes exceedingly rare.

3.2 | Pathophysiology

Despite the paucity of MSP2 and three cases, there is compelling functional data to argue for its common pathogenicity to the other MSP syndromes. hnRNP complexes, formed by RNA binding proteins (RBPs) coupled with RNAs, control RNA processing, transcription, splicing, translation, sequestration, and degradation. RBPs of hnRNPs contain a conserved low complexity domain (LCD), also called prion-like domain, that functions to mediate stress granule formation.[66] Normally stress granules dissolve after cellular stress passes, but stress granules formed by mutant RBPs remain insoluble and consequently sequester wild-type RBPs, resulting in irreversible toxic aggregates. Whether the neurodegeneration that results is due to toxic gain of function from stress granules, or due to loss of function of trapped proteins, remains unclear, but it may be a combination of both.[67]

Additional evidence for the hnRNPs' pathogenicity in MSP lies in hnRNPA2B1 and hnRNPA1's direct interaction with TDP-43 via their C-terminal glycine-rich domains, working together to mediate RNA metabolism.[2,68] Both hnRNPs are prone to fibrillization, and disease mutations accelerate this process by inducing potent steric zippers; ultimately, this serves to accelerate nucleation and polymerization, alter dynamics of RNA granule assembly, and disrupt RNA metabolism.[2]

4 | MSP4: SQSTM1

In 2015, Bucelli et al. used whole exome sequencing to identify mutations in *SQSTM1* (encoding sequestosome 1, also known as the ubiquitin-binding protein p62) in a family who had autosomal dominant IBM that appeared similar to that seen with *VCP*, *hnRNPA1B1*, and *hnRNPA1* mutations.[10] This family had late onset distal lower extremity muscle weakness, and muscle pathology showed rimmed vacuoles and inclusions of TDP-43 and SQSTM1. Various mutations of *SQSTM1* have been linked to IBM, as well as ALS, FTD, and PDB, leading to this gene being termed MSP4.

4.1 | Clinical features

Mutations in *SQSTM1* are frequently seen in PDB,[4] and rarely have been reported to associate with sporadic and familial ALS and FTD.[69] They are found in 40% of familial PDB and 10% of sporadic PDB.[63] Given its association with a rimmed vacuolar myopathy in addition to the ALS, FTD, and PDB, it was recently proposed that SQSTM1 be considered MSP4.[10] The IBM has been seen both in isolation and in combination with PDB, and the FTD has been seen both in isolation and in combination with ALS.[23] It remains unclear why most patients with *SQSTM1* mutations develop PDB, and some go on to develop myopathy, ALS, or FTD, but there may be susceptibility alleles in other genes that render certain organ systems more likely to become involved.[10]

4.2 | Pathophysiology

SQSTM1 is found in neuronal and glial ubiquitin-positive inclusions in various tauopathy and synucleinopathy neurodegenerative conditions. In FTD and ALS-FTD, it co-localizes with TDP-43 and fused in sarcoma (FUS) in the brain and spinal cord.[70,71]

P62/SQSTM1 is an adaptor that interacts with ubiquinated proteins and LC3 (microtubule-associated protein 1A light chain-3) through its ubiquitin-associated (UBA) and LC3-associated domains to mediate autophagic degradation. It then oligomerizes and interacts with neighbor of BRCA1 gene 1 (Nbr1), another ubiquitin adaptor.[72] These sometimes work together to conduct autophagic degradation of proteins.[73] P62/SQSTM1 also plays a role in antioxidant response pathways, mTORC1 activity, protein turnover, and autophagic turnover of nicotinic acetylcholine receptors in muscle.[74-77] Most disease-causing mutations in *SQSTM1* are missense mutations or truncations of the UBA domain, resulting in impaired protein homeostasis and disruption of autophagic degradation of ubiquinated proteins.[78] Rare UBA domain mutations correlate with widespread neuronal and glial phospho-TDP-43 pathology, and can double the risk for development of FTD.[79] *SQSTM1* mutations promote osteoclast formation by enhancing receptor activation of NF-κB (RANK), causing abnormal protein to accumulate in the endoplasmic reticulum (ER) through the unfolded protein response.

5 | MSP5: MATR3

Mutations in the matrin 3 gene (*MATR3*), which encodes an RBP associated with TDP-43, have been seen in familial ALS, FTD, and IBM.[80] MATR3-related neurodegeneration has been implicated as an MSP given its overlapping molecular pathogenesis and clinical phenotypes with MSP2 and MSP3.[6]

5.1 | Clinical features

In 2015, Lin et al. described a bulbar-onset patient with ALS with a *MATR3* mutation, conducted the relevant literature review, and suggested that this mutation met criteria to stand alongside other MSPs.[6,81] However, it is unclear whether it is seen in PDB as yet, so the classification as MSP5 is not yet widespread or well established.[80,82,83]

MATR3 mutations were originally identified as causative in vocal cord and pharyngeal weakness with distal myopathy (VCPDM),[84,85] in patients who had a dominant pattern of slowly progressive asymmetric weakness and concomitant vocal cord paralysis.[86] It was then identified in patients with familial ALS with dementia by whole exome sequencing,[80] before later being associated with MSP and distal onset myopathy without vocal cord paralysis. Overall, the incidence of *MATR3* mutations in familial ALS and ALS-FTD remains rare.[87,88] A study of 16 patients from six German families with *MATR3* mutations found that individuals had predominantly distal weakness, most

severely affecting wrist and finger extensors and ankle dorsiflexion, but six had proximal and axial weakness, five had respiratory weakness, six had dysphagia, and seven had mild voice abnormalities, although none had vocal cord dysfunction on laryngoscopy.[85] Muscle biopsies in the German study demonstrated mild to severe dystrophic changes, vacuoles, and absence of sarcomeres in the perinuclear region.[85] Whole-body muscle MRI performed on 15 *MATR3*-associated distal myopathy patients demonstrated distinct findings: distal legs were predominantly affected with severe fatty infiltration, especially of the gastrocnemius and soleus; of note, there was also preferential involvement of the semimembranosus, biceps femoris, gluteus minimus, and thoracic axial muscles, which are less commonly involved in other distal myopathies.[89]

5.2 | Pathophysiology

Matrin 3 is a component of the nuclear matrix, which is proteinaceous scaffolding throughout the nuclei of skeletal muscle tissue.[86] This matrix is vital for RNA processing related to skeletal muscle structure and function, and when disrupted can result in myofiber degeneration.[90] MATR3's two RNA binding domains are homologous to those of hnRNPs L and I.[91] It also interacts with TDP-43, FUS, hnRNPA1 and hnRNA2B1, all of which have been associated with ALS or MSP.[64,92]

Transgenic mice overexpressing mutant MATR3 were found to have myopathic changes including fiber size variation and rimmed vacuoles, reduced motor neurons in spinal cord histology, activation of microglia and astrocytes, and clinically had reduced body weight and motor activity.[11] Proteomic analysis of their muscle showed upregulation of proteins associated with chaperones including p62, stress response, protein degradation, and nuclear metabolism, as can be seen in other forms of MSP.[11]

6 | TIA1

Mutations in stress granule protein T-cell restricted intracellular antigen 1 (*TIA1*) are typically associated with Welander distal myopathy, but have also been associated with IBM, FTD, and ALS, but not PDB, so it may be considered part of the MSP continuum by some as well. In addition, TIA1 mutations have similar pathophysiologic implications as the other MSP syndromes. Adequate data for this gene as it applies to MSP is still lacking, however, and cases remain rare.

6.1 | Clinical features

A founder mutation of *TIA1* was described in Swedish and Finnish patients, causing Welander distal myopathy, a rimmed vacuolar myopathy with clinical and histological similarity to the myopathy seen in MSP1-5.[93,94] In 2017, Mackenzie et al. used whole exome sequencing to identify *TIA1* mutations in a family with dominantly inherited ALS-FTD, in whom autopsy confirmed TDP-43 pathology.[83] The same year, a cohort of 1039 ALS and ALS-FTD patients were analyzed for *TIA1* mutations in the gene's LCD, and nine mutation carriers were identified, representing 2.2% of familial ALS in this case.[93] Of these patients, the phenotype was characterized by frequent bulbar onset weakness and expressive aphasia, an absence of parkinsonism or psychotic features, and autosomal dominant inheritance, although some cases lacked positive family history, suggesting variable penetrance.[93] Post-mortem neuropathological analysis of ALS-FTD patients with *TIA1* mutations revealed widespread TDP-43 accumulation, while lower motor neurons had higher amounts of round eosinophilic and Lewy-body like inclusions.[93]

6.2 | Pathophysiology

TIA1 encodes an RNA-binding protein with an LCD, similar to TDP-43, FUS, and hnRNPA1. It is an important component of stress granules, so mutations in the LCD of TIA1 can disrupt stress granule clearance, in addition to promoting stress granule assembly by liquid–liquid phase separation.[83,94] The accumulation of such stress granules results in aggregated TDP-43, which becomes immobile and insoluble.[83] Additionally, TIA1 knockdown has been shown to inhibit the protein tau from its misfolding and toxicity, and TIA1 and tau synergistically act to modulate neurodegeneration as seen in ALS and FTD.[95]

Digenic mutations of both a *TIA1*-N357S variant and *SQSTM1* pathogenic mutation have resulted in a distal myopathy with rimmed vacuole IBM pathology, linking stress granule homeostasis and ubiquitin-dependent autophagic degradation and suggesting an oligogenic mechanism for the neurodegeneration.[82] This theory was supported by the finding that myoblasts expressing both the *TIA1*-N357S variant and a *SQSTM1*-A390X mutation had synergistic myotoxicity compared to control myoblasts.[82]

7 | OPTN

OPTN, an adaptor required for ubiquitin-dependent autophagy, is also implicated in the neurodegeneration of ALS, FTD, and PDB, thus ultimately has been included under the umbrella of MSP by some scientists.[96,97]

7.1 | Clinical features

Mutations in *OPTN*, primarily through loss of function, are responsible for over 1% of familial ALS cases, although they were originally associated with autosomal dominant primary open angle glaucoma.[96,98,99] Mutant OPTN associated with ubiquinated inclusions is found in familial ALS attributed to OPTN mutation, while wild type misfolded OPTN is seen in sporadic ALS.[100] Wild-type OPTN is also seen in pathogenic inclusions of other neurodegenerative diseases including

Alzheimer, Parkinson, Huntington, multiple system atrophy, and Creutzfeld–Jacob diseases.[101,102] OPTN-associated ALS and ALS-FTD may be associated with a more aggressive course of disease, with earlier mortality.[99]

Patients with sporadic IBM and OPMD were found to have cytoplasmic TDP-43 and OPTN more frequently than patients with polymyositis, dermatomyositis, or neurogenic muscular atrophy, suggesting that OPTN's predisposition to colocalize with TDP-43 may play a role in the pathogenesis of myopathy with rimmed vacuoles,[103] although further data about OPTN as a cause for myopathy is lacking.

Genetic variants of *OPTN* have been identified in PDB in several populations and pathophysiological links have been proposed, although a direct causal relationship has not yet been established.[104,105] To date, there have not been reported cases of OPTN-associated ALS co-occurring with PDB.[23]

7.2 | Pathophysiology

OPTN is a protein that plays a role in cellular trafficking and autophagy. Specifically, it functions as an autophagy receptor that binds to protein aggregates and microtubule associated protein 1A/1B-light chain 3.[106,107] As autophagosomes interact with ER and Golgi compartments, impaired cellular trafficking can provoke ER stress and an unfolded protein response.[108] ER stress and impaired intracellular trafficking, including dysfunctional fusion of the autophagosomes to lysosomes, are pathologic features of ALS.[109] It also mediates NFκB signaling, a known regulator of osteoclast differentiation[5]; thus, mutations of *OPTN* can predispose to PDB development similarly to *SQSTM1*.

8 | DISCUSSION

As knowledge and awareness increase about MSP and testing becomes more accessible, more patients will be diagnosed who are currently misdiagnosed with related disorders or are not recognized as having a syndrome of multi-organ involvement.[36] Individuals with MSP have wide phenotypic heterogeneity and variable penetrance at the intra- and interfamilial level, which likely results from pleiotropy and perhaps other various cellular and environmental factors. The most common features, however, include myopathy, bone disease, dementia, and/or motor neuron involvement. Most of the MSP subtypes also share similar histopathology, with prominent ubiquitin and fibrillar TDP-43 accumulation in the cytoplasm. The intersection of the mechanistic pathways of *VCP*, *hnRNPA2B1*, *hnRNPA1*, *SQSTM1*, *MATR3*, *TIA1*, and *OPTN* helps to unify MSP as a spectrum syndrome. MSP appears to stem from a common molecular pathogenesis resulting from disruption of the two major protein clearance pathways, the UPS and autophagy, which are the same pathways that are disrupted in ALS and inclusion body myopathy. The importance of TDP-43 in pathogenesis was confirmed by the identification of mutations in the gene encoding this RNA-binding protein.[110] Disruption of these pathways results in altered RNA granule homeostasis, TDP-43 accumulation and mislocalization, and impaired mitochondrial function and mitophagy, which ultimately tie together multi-organ degeneration. Determining a way to restore properly functioning RNA granules in order to counter these mostly dominantly inherited mutations could have broad implications for various age-related degenerative conditions with a potentially common modifier of the pathogenesis.

Strategies to activate autophagy and the UPS have been studied for their potential role in treating ALS and FTD,[111] and could similarly be applied to MSP as a whole. In particular, the disease burden caused by aggregates of TDP-43 could be ameliorated by promoting UPS function, and this could be further boosted by enhancing autophagy.[111] Using autophagy to remove damaged mitochondria and protein aggregates has been shown to help slow motor neuron disease.[112-114] However, targeting autophagy has not always worked in motor neuron disease, and in some cases, can even worsen function.[115-118] The mammalian target of rapamycin (mTOR) pathway, which negatively regulates autophagy, has had mixed results as to the benefit in VCP mice models.[119-122] Other agents known to modify autophagy, including trehalose, lithium, and Withaferin A, have also shown varying results in ALS models.[115,123,124] A more selective and nuanced method of enhancing autophagy, and understanding what other quality-control pathways are playing a role, would be essential for unlocking a remedy for the neurodegeneration in MSP.

Another potential treatment tactic for MSP lies in NF-κB inhibitors, since NF-κB is implicated in the pathogenesis of PDB as well as muscle disease.[125] Overactive mutated VCP can promote activation of NF-κB,[126] subsequently increasing osteoclast formation and muscle damage. In Duchenne muscular dystrophy, preclinical studies of NF-κB inhibitors improved muscle regeneration and function in mice and dog models,[127] and blocked NF-κB pathways in patients after 1 wk of treatment.[128] This same concept could potentially be applied to the NF-κB mediated muscle and bone degeneration seen in MSP.

A major challenge with doing therapeutic trials in MSP is the lack of natural history and reliable biomarkers that can be used to understand disease progression and predict treatment response. Given the rarity of this disease, no single center has enough patients to perform a large longitudinal study of disease progression. It is unclear whether there are differences in tau-based nuclear imaging characteristics between MSP related FTD vs. non-MSP related, and whether they can be reliably used in a natural history studies or therapeutic trials. There is prominent TDP-43 pathology in MSP, but we do not have information on TDP-43 levels in blood, skin, or platelet assays in relation to disease and whether they can serve as a reliable biomarker. At this time, much remains to be discovered regarding the incidence and penetrance of MSP. It will be important to establish a reliable natural history cohort and validate patient related outcome measures in order to design effective clinical trials. However, the rarity of the MSP as an entity will render such data collection and follow up measures challenging. Consideration should be given to innovative virtual ways of conducting these visits and collecting these data.

ACKNOWLEDGEMENTS

We sincerely appreciate the muscle pathology photomicrographs provided by Conrad Chris Weihl, MD, PhD (Washington University in St. Louis, MO).

CONFLICTS OF INTEREST

Dr. Korb has served on advisory boards for Biogen, Argenx, and CSL Behring. She has also served on the speaker's bureau for Biogen. In relation to these activities, she has received travel reimbursement and honoraria. Dr. Kimonis does not have any conflicts of interest to disclose. Dr. Mozaffar has served on advisory boards for Abbvie, Alexion, Amicus, Argenx, Audentes, Sanofi-Genzyme, Sarepta, Spark Therapeutics. In relation to these activities, he has received travel reimbursement and honoraria. He has also served on the speaker's bureau for Alexion, CSL, Grifols, and Sanofi-Genzyme. Dr. Mozaffar serves on the medical advisory board for the Myositis Association, Neuromuscular Disease Foundation, Myasthenia Gravis Foundation of California, and Myasthenia Gravis Foundation of America, and has received travel funding from the Myositis Association and the Neuromuscular Disease Foundation. Dr. Mozaffar receives research funding from the Myositis Association, the Muscular Dystrophy Association, the National Institutes for Health and from the following sponsors: Alexion, Amicus, Argenx, Audentes, Bristol-Myers-Squib, Cartesian Therapeutics, Grifols, Momenta, Ra Pharmaceuticals, Sanofi-Genzyme, Spark Therapeutics, UCB, and Valerion. He serves on the data safety monitoring board for Acceleron.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCE

1. 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.
2. 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.
3. Laurin N, Brown JP, Morissette J, Raymond V. Recurrent mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget disease of bone. *Am J Hum Genet*. 2002;70:1582-1588.
4. Hocking LJ, Lucas GJ, Daroszewska A, et al. Domain-specific mutations in sequestosome 1 (SQSTM1) cause familial and sporadic Paget's disease. *Hum Mol Genet*. 2002;11:2735-2739.
5. Obaid R, Wani SE, Azfer A, et al. Optineurin negatively regulates osteoclast differentiation by modulating NF-kappaB and interferon signaling: implications for Paget's disease. *Cell Rep*. 2015;13:1096-1102.
6. Taylor JP. Multisystem proteinopathy: intersecting genetics in muscle, bone, and brain degeneration. *Neurology*. 2015;85:658-660.
7. Llewellyn K, Nalbandian A, Camacho-Vanegas O, et al. Clinical characterization of myopathy in a rare autosomal disease: hereditary bone dysplasia/osteosarcoma and limb girdle myopathy in a unique family. *J Rare Disord*. 2014;3:32-37.
8. van de Warrenburg BP, Schouten MI, de Bot ST, et al. Clinical exome sequencing for cerebellar ataxia and spastic paraplegia uncovers novel gene-disease associations and unanticipated rare disorders. *Eur J Hum Genet*. 2016;24:1460-1466.
9. Benatar M, Wuu J, Fernandez C, et al. Motor neuron involvement in multisystem proteinopathy: implications for ALS. *Neurology*. 2013;80:1874-1880.
10. Bucelli RC, Arhzaouy K, Pestronk A, et al. SQSTM1 splice site mutation in distal myopathy with rimmed vacuoles. *Neurology*. 2015;85:665-674.
11. Zhang X, Yamashita S, Hara K, et al. A mutant MATR3 mouse model to explain multisystem proteinopathy. *J Pathol*. 2019;249:182-192.
12. Evangelista T, Weihl CC, Kimonis V, Lochmuller H, VCPrd C. 215th ENMC international workshop VCP-related multi-system proteinopathy (IBMPFD) 13-15 November 2015, Heemskerk, The Netherlands. *Neuromuscul Disord*. 2016;26:535-547.
13. Monahan Z, Shewmaker F, Pandey UB. Stress granules at the intersection of autophagy and ALS. *Brain Res*. 2016;1649:189-200.
14. Weihl CC, Temiz P, Miller SE, et al. TDP-43 accumulation in inclusion body myopathy muscle suggests a common pathogenic mechanism with frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 2008;79:1186-1189.
15. Salajegheh M, Pinkus JL, Taylor JP, et al. Sarcoplasmic redistribution of nuclear TDP-43 in inclusion body myositis. *Muscle Nerve*. 2009;40:19-31.
16. Pinkus JL, Amato AA, Taylor JP, Greenberg SA. Abnormal distribution of heterogeneous nuclear ribonucleoproteins in sporadic inclusion body myositis. *Neuromuscul Disord*. 2014;24:611-616.
17. De Ridder W, Azmi A, Clemen CS, et al. Multisystem proteinopathy due to a homozygous p.Arg159His VCP mutation: a tale of the unexpected. *Neurology*. 2019;94(8):e785-e796.
18. Kazamel M, Sorenson EJ, McEvoy KM, et al. Clinical spectrum of valosin containing protein (VCP)-opathy. *Muscle Nerve*. 2016;54:94-99.
19. Mehta SG, Khare M, Ramani R, et al. Genotype-phenotype studies of VCP-associated inclusion body myopathy with Paget disease of bone and/or frontotemporal dementia. *Clin Genet*. 2013;83:422-431.
20. Figueroa-Bonaparte S, Hudson J, Barresi R, et al. Mutational spectrum and phenotypic variability of VCP-related neurological disease in the UK. *J Neurol Neurosurg Psychiatry*. 2016;87:680-681.
21. Vallet M, Ralston SH. Biology and treatment of Paget's disease of bone. *J Cell Biochem*. 2016;117:289-299.
22. Appelman-Dijkstra NM, Papapoulos SE. Paget's disease of bone. *Best Pract Res Clin Endocrinol Metab*. 2018;32:657-668.
23. Ralston SH, Taylor JP. Rare inherited forms of Paget's disease and related syndromes. *Calcif Tissue Int*. 2019;104:501-516.
24. Forman MS, Mackenzie IR, Cairns NJ, et al. Novel ubiquitin neuropathology in frontotemporal dementia with valosin-containing protein gene mutations. *J Neuropathol Exp Neurol*. 2006;65:571-581.
25. Cairns NJ, Neumann M, Bigio EH, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. *Am J Pathol*. 2007;171:227-240.
26. Neumann M, Mackenzie IR, Cairns NJ, et al. TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. *J Neuropathol Exp Neurol*. 2007;66:152-157.
27. McBride TI. Paget's disease and muscular dystrophy. Report of an unusual association in one family. *Scott Med J*. 1966;11:238-243.
28. Tucker WS Jr, Hubbard WH, Stryker TD, et al. A new familial disorder of combined lower motor neuron degeneration and skeletal disorganization. *Trans Assoc Am Physicians*. 1982;95:126-134.
29. 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.

30. Kovach MJ, Waggoner B, Leal SM, et al. Clinical delineation and localization to chromosome 9p13.3-p12 of a unique dominant disorder in four families: hereditary inclusion body myopathy, Paget disease of bone, and frontotemporal dementia. *Mol Genet Metab*. 2001; 74:458-475.
31. Waggoner B, Kovach MJ, Winkelman M, et al. Heterogeneity in familial dominant Paget disease of bone and muscular dystrophy. *Am J Med Genet*. 2002;108:187-191.
32. Le Ber I, Van Bortel I, Nicolas G, et al. hnRNPA2B1 and hnRNPA1 mutations are rare in patients with "multisystem proteinopathy" and frontotemporal lobar degeneration phenotypes. *Neurobiol Aging*. 2014;35:934 e935-934 e936.
33. 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.
34. Hubbers CU, Clemen CS, Kesper K, et al. Pathological consequences of VCP mutations on human striated muscle. *Brain*. 2007;130: 381-393.
35. Chan N, Le C, Shieh P, et al. Valosin-containing protein mutation and Parkinson's disease. *Parkinsonism Relat Disord*. 2012;18: 107-109.
36. Kimonis VE, Mehta SG, Fulchiero EC, et al. Clinical studies in familial VCP myopathy associated with Paget disease of bone and frontotemporal dementia. *Am J Med Genet A*. 2008;146A:745-757.
37. Miller TD, Jackson AP, Barresi R, et al. Inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD): clinical features including sphincter disturbance in a large pedigree. *J Neurol Neurosurg Psychiatry*. 2009;80:583-584.
38. Mehta SG, Watts GD, Adamson JL, et al. APOE is a potential modifier gene in an autosomal dominant form of frontotemporal dementia (IBMPFD). *Genet Med*. 2007;9:9-13.
39. Gu JM, Ke YH, Yue H, et al. A novel VCP mutation as the cause of atypical IBMPFD in a Chinese family. *Bone*. 2013;52:9-16.
40. Shi Z, Hayashi YK, Mitsuhashi S, et al. Characterization of the Asian myopathy patients with VCP mutations. *Eur J Neurol*. 2012;19: 501-509.
41. 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.
42. Fanganiello RD, Kimonis VE, Corte CC, Nitrini R, Passos-Bueno MR. A Brazilian family with hereditary inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia. *Braz J Med Biol Res*. 2011;44:374-380.
43. Gonzalez-Perez P, Cirulli ET, Drory VE, et al. Novel mutation in VCP gene causes atypical amyotrophic lateral sclerosis. *Neurology*. 2012; 79:2201-2208.
44. Kumar KR, Needham M, Mina K, et al. Two Australian families with inclusion-body myopathy, Paget's disease of bone and frontotemporal dementia: novel clinical and genetic findings. *Neuromuscul Disord*. 2010;20:330-334.
45. van den Boom J, Meyer H. VCP/p97-mediated unfolding as a principle in protein homeostasis and signaling. *Mol Cell*. 2018;69:182-194.
46. Rodriguez-Ortiz CJ, Flores JC, Valenzuela JA, et al. The myoblast C2C12 transfected with mutant Valosin-containing protein exhibits delayed stress granule resolution on oxidative stress. *Am J Pathol*. 2016;186:1623-1634.
47. Al-Tahan S, Al-Obeidi E, Yoshioka H, et al. Novel valosin-containing protein mutations associated with multisystem proteinopathy. *Neuromuscul Disord*. 2018;28:491-501.
48. Buchan JR, Kolaitis RM, Taylor JP, Parker R. Eukaryotic stress granules are cleared by autophagy and Cdc48/VCP function. *Cell*. 2013; 153:1461-1474.
49. Meyer H, Weihl CC. The VCP/p97 system at a glance: connecting cellular function to disease pathogenesis. *J Cell Sci*. 2014;127:3877-3883.
50. Niwa H, Ewens CA, Tsang C, Yeung HO, Zhang X, Freemont PS. The role of the N-domain in the ATPase activity of the mammalian AAA ATPase p97/VCP. *J Biol Chem*. 2012;287:8561-8570.
51. Fernandez-Saiz V, Buchberger A. Imbalances in p97 co-factor interactions in human proteinopathy. *EMBO Rep*. 2010;11:479-485.
52. Durmus H, Ayhan O, Cirak S, et al. Neuromuscular endplate pathology in recessive desminopathies: lessons from man and mice. *Neurology*. 2016;87:799-805.
53. Rudolf G, Suominen T, Penttila S, et al. Homozygosity of the dominant Myotilin c.179C>T (p.Ser60Phe) mutation causes a more severe and proximal muscular dystrophy. *J Neuromuscul Dis*. 2016;3: 275-281.
54. Muller JM, Deinhardt K, Rosewell I, Warren G, Shima DT. Targeted deletion of p97 (VCP/CDC48) in mouse results in early embryonic lethality. *Biochem Biophys Res Commun*. 2007;354:459-465.
55. Weihl CC, Miller SE, Hanson PI, Pestronk A. Transgenic expression of inclusion body myopathy associated mutant p97/VCP causes weakness and ubiquitinated protein inclusions in mice. *Hum Mol Genet*. 2007;16:919-928.
56. Custer SK, Neumann M, Lu H, Wright AC, Taylor JP. Transgenic mice expressing mutant forms VCP/p97 recapitulate the full spectrum of IBMPFD including degeneration in muscle, brain and bone. *Hum Mol Genet*. 2010;19:1741-1755.
57. Badadani M, Nalbandian A, Watts GD, et al. VCP associated inclusion body myopathy and Paget disease of bone knock-in mouse model exhibits tissue pathology typical of human disease. *PLoS One*. 2010;5(10, e13183):1-15.
58. Nalbandian A, Llewellyn KJ, Badadani M, et al. A progressive translational mouse model of human valosin-containing protein disease: the VCP(R155H/+) mouse. *Muscle Nerve*. 2013;47:260-270.
59. Zhang T, Mishra P, Hay BA, Chan D, Guo M. Valosin-containing protein (VCP/p97) inhibitors relieve Mitofusin-dependent mitochondrial defects due to VCP disease mutants. *Elife*. 2017;6:e17834.
60. Llewellyn KJ, Nalbandian A, Weiss LN, et al. Myogenic differentiation of VCP disease-induced pluripotent stem cells: a novel platform for drug discovery. *PLoS One*. 2017;12:e0176919.
61. Wang B, Maxwell BA, Joo JH, et al. ULK1 and ULK2 regulate stress granule disassembly through phosphorylation and activation of VCP/p97. *Mol Cell*. 2019;74:742-757 e748.
62. Ahmed M, Machado PM, Miller A, Spicer C, Herbelin L, He J, et al. Targeting protein homeostasis in sporadic inclusion body myositis. *Sci Transl Med* 2016; 8:331ra341.
63. Qi X, Pang Q, Wang J, et al. Familial early-onset Paget's disease of bone associated with a novel hnRNPA2B1 mutation. *Calcif Tissue Int*. 2017;101:159-169.
64. Taylor JP, Brown RH Jr, Cleveland DW. Decoding ALS: from genes to mechanism. *Nature*. 2016;539:197-206.
65. Naruse H, Ishiura H, Mitsui J, et al. Molecular epidemiological study of familial amyotrophic lateral sclerosis in Japanese population by whole-exome sequencing and identification of novel HNRNPA1 mutation. *Neurobiol Aging*. 2018;61:255 e259-255 e216.
66. Lee KH, Zhang P, Kim HJ, et al. C9orf72 dipeptide repeats impair the assembly, dynamics, and function of membrane-less organelles. *Cell*. 2016;167:774-788 e717.
67. Baradaran-Heravi Y, Van Broeckhoven C, van der Zee J. Stress granule mediated protein aggregation and underlying gene defects in the FTD-ALS spectrum. *Neurobiol Dis*. 2019;134:104639.
68. Buratti E, Brindisi A, Giombi M, Tisminetzky S, Ayala YM, Baralle FE. TDP-43 binds heterogeneous nuclear ribonucleoprotein a/B through its C-terminal tail: an important region for the inhibition of cystic fibrosis transmembrane conductance regulator exon 9 splicing. *J Biol Chem*. 2005;280:37572-37584.
69. Fecto F, Yan J, Vemula SP, et al. SQSTM1 mutations in familial and sporadic amyotrophic lateral sclerosis. *Arch Neurol*. 2011;68:1440-1446.

70. Arai T, Nonaka T, Hasegawa M, et al. Neuronal and glial inclusions in frontotemporal dementia with or without motor neuron disease are immunopositive for p62. *Neurosci Lett*. 2003;342:41-44.
71. Deng HX, Zhai H, Bigio EH, et al. FUS-immunoreactive inclusions are a common feature in sporadic and non-SOD1 familial amyotrophic lateral sclerosis. *Ann Neurol*. 2010;67:739-748.
72. Lamark T, Perander M, Outzen H, et al. Interaction codes within the family of mammalian Phox and Bem1p domain-containing proteins. *J Biol Chem*. 2003;278:34568-34581.
73. Kirkin V, Lamark T, Sou YS, et al. A role for NBR1 in autophagosomal degradation of ubiquitinated substrates. *Mol Cell*. 2009;33:505-516.
74. Komatsu M, Kurokawa H, Waguri S, et al. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. *Nat Cell Biol*. 2010;12:213-223.
75. Duran A, Amanchy R, Linares JF, et al. p62 is a key regulator of nutrient sensing in the mTORC1 pathway. *Mol Cell*. 2011;44:134-146.
76. Lange S, Xiang F, Yakovenko A, et al. The kinase domain of titin controls muscle gene expression and protein turnover. *Science*. 2005;308:1599-1603.
77. Khan MM, Strack S, Wild F, et al. Role of autophagy, SQSTM1, SH3GLB1, and TRIM63 in the turnover of nicotinic acetylcholine receptors. *Autophagy*. 2014;10:123-136.
78. Rea SL, Majcher V, Searle MS, Layfield R. SQSTM1 mutations: bridging Paget disease of bone and ALS/FTLD. *Exp Cell Res*. 2014;325:27-37.
79. van der Zee J, Van Langenhove T, Kovacs GG, et al. Rare mutations in SQSTM1 modify susceptibility to frontotemporal lobar degeneration. *Acta Neuropathol*. 2014;128:397-410.
80. Johnson JO, Pioro EP, Boehringer A, et al. Mutations in the Matrin 3 gene cause familial amyotrophic lateral sclerosis. *Nat Neurosci*. 2014;17:664-666.
81. Lin KP, Tsai PC, Liao YC, et al. Mutational analysis of MATR3 in Taiwanese patients with amyotrophic lateral sclerosis. *Neurobiol Aging*. 2015;36:e2001-e2004.
82. Lee Y, Jonson PH, Sarparanta J, et al. TIA1 variant drives myodegeneration in multisystem proteinopathy with SQSTM1 mutations. *J Clin Invest*. 2018;128:1164-1177.
83. Mackenzie IR, Nicholson AM, Sarkar M, et al. TIA1 mutations in amyotrophic lateral sclerosis and Frontotemporal dementia promote phase separation and Alter stress granule dynamics. *Neuron*. 2017;95:808-816 e809.
84. Feit H, Silbergleit A, Schneider LB, et al. Vocal cord and pharyngeal weakness with autosomal dominant distal myopathy: clinical description and gene localization to 5q31. *Am J Hum Genet*. 1998;63:1732-1742.
85. 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.
86. Senderek J, Garvey SM, Krieger M, et al. Autosomal-dominant distal myopathy associated with a recurrent missense mutation in the gene encoding the nuclear matrix protein, matrin 3. *Am J Hum Genet*. 2009;84:511-518.
87. Fifita JA, Williams KL, McCann EP, et al. Mutation analysis of MATR3 in Australian familial amyotrophic lateral sclerosis. *Neurobiol Aging*. 2015;36:e1601-e1602.
88. Millecamps S, De Septenville A, Teyssou E, et al. Genetic analysis of matrin 3 gene in French amyotrophic lateral sclerosis patients and frontotemporal lobar degeneration with amyotrophic lateral sclerosis patients. *Neurobiol Aging*. 2014;35:2882 e2813-2882 e2815.
89. Mensch A, Kraya T, Koester F, Muller T, Stoevesandt D, Zierz S. Whole-body muscle MRI of patients with MATR3-associated distal myopathy reveals a distinct pattern of muscular involvement and highlights the value of whole-body examination. *J Neurol*. 2020;267:2408-2420.
90. Iradi MCG, Triplett JC, Thomas JD, et al. Characterization of gene regulation and protein interaction networks for Matrin 3 encoding mutations linked to amyotrophic lateral sclerosis and myopathy. *Sci Rep*. 2018;8:4049.
91. Hakes DJ, Berezney R. Molecular cloning of matrin F/G: a DNA binding protein of the nuclear matrix that contains putative zinc finger motifs. *Proc Natl Acad Sci U S A*. 1991;88:6186-6190.
92. Hein MY, Hubner NC, Poser I, et al. A human interactome in three quantitative dimensions organized by stoichiometries and abundances. *Cell*. 2015;163:712-723.
93. Hirsch-Reinshagen V, Pottier C, Nicholson AM, et al. Clinical and neuropathological features of ALS/FTD with TIA1 mutations. *Acta Neuropathol Commun*. 2017;5:96.
94. Hackman P, Sarparanta J, Lehtinen S, et al. Welander distal myopathy is caused by a mutation in the RNA-binding protein TIA1. *Ann Neurol*. 2013;73:500-509.
95. Vanderweyde T, Apicco DJ, Youmans-Kidder K, et al. Interaction of tau with the RNA-binding protein TIA1 regulates tau pathophysiology and toxicity. *Cell Rep*. 2016;15:1455-1466.
96. Maruyama H, Morino H, Ito H, et al. Mutations of optineurin in amyotrophic lateral sclerosis. *Nature*. 2010;465:223-226.
97. Korac J, Schaeffer V, Kovacevic I, et al. Ubiquitin-independent function of optineurin in autophagic clearance of protein aggregates. *J Cell Sci*. 2013;126:580-592.
98. Rezaie T, Child A, Hitchings R, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science*. 2002;295:1077-1079.
99. Feng SM, Che CH, Feng SY, et al. Novel mutation in optineurin causing aggressive ALS+/−frontotemporal dementia. *Ann Clin Transl Neurol*. 2019;6:2377-2383.
100. Deng HX, Bigio EH, Zhai H, et al. Differential involvement of optineurin in amyotrophic lateral sclerosis with or without SOD1 mutations. *Arch Neurol*. 2011;68:1057-1061.
101. Osawa T, Mizuno Y, Fujita Y, Takatama M, Nakazato Y, Okamoto K. Optineurin in neurodegenerative diseases. *Neuropathology*. 2011;31:569-574.
102. Ayaki T, Ito H, Komure O, et al. Multiple Proteinopathies in familial ALS cases with Optineurin mutations. *J Neuropathol Exp Neurol*. 2018;77:128-138.
103. Yamashita S, Kimura E, Tawara N, et al. Optineurin is potentially associated with TDP-43 and involved in the pathogenesis of inclusion body myositis. *Neuropathol Appl Neurobiol*. 2013;39:406-416.
104. Silva IAL, Conceicao N, Gagnon E, et al. Effect of genetic variants of OPTN in the pathophysiology of Paget's disease of bone. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864:143-151.
105. Silva IAL, Conceicao N, Gagnon E, Brown JP, Cancela ML, Michou L. Molecular effect of an OPTN common variant associated to Paget's disease of bone. *PLoS One*. 2018;13:e0197543.
106. Tumbarello DA, Waxse BJ, Arden SD, Bright NA, Kendrick-Jones J, Buss F. Autophagy receptors link myosin VI to autophagosomes to mediate Tom1-dependent autophagosome maturation and fusion with the lysosome. *Nat Cell Biol*. 2012;14:1024-1035.
107. Wild P, Farhan H, McEwan DG, et al. Phosphorylation of the autophagy receptor optineurin restricts salmonella growth. *Science*. 2011;333:228-233.
108. Preston AM, Gurisik E, Bartley C, Laybutt DR, Biden TJ. Reduced endoplasmic reticulum (ER)-to-Golgi protein trafficking contributes to ER stress in lipotoxic mouse beta cells by promoting protein overload. *Diabetologia*. 2009;52:2369-2373.
109. Sundaramoorthy V, Walker AK, Tan V, et al. Defects in optineurin- and myosin VI-mediated cellular trafficking in amyotrophic lateral sclerosis. *Hum Mol Genet*. 2015;24:3830-3846.
110. Sreedharan J, Blair IP, Tripathi VB, et al. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science*. 2008;319:1668-1672.

111. Scotter EL, Vance C, Nishimura AL, et al. Differential roles of the ubiquitin proteasome system and autophagy in the clearance of soluble and aggregated TDP-43 species. *J Cell Sci*. 2014;127:1263-1278.
112. Crippa V, Sau D, Rusmini P, et al. The small heat shock protein B8 (HspB8) promotes autophagic removal of misfolded proteins involved in amyotrophic lateral sclerosis (ALS). *Hum Mol Genet*. 2010;19:3440-3456.
113. Hetz C, Thielen P, Matus S, et al. XBP-1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy. *Genes Dev*. 2009;23:2294-2306.
114. Xie Y, Zhou B, Lin MY, Wang S, Foust KD, Sheng ZH. Endolysosomal deficits augment mitochondria pathology in spinal motor neurons of asymptomatic fALS mice. *Neuron*. 2015;87:355-370.
115. Fornai F, Longone P, Cafaro L, et al. Lithium delays progression of amyotrophic lateral sclerosis. *Proc Natl Acad Sci U S A*. 2008;105:2052-2057.
116. Perera ND, Sheean RK, Lau CL, et al. Rilmenidine promotes MTOR-independent autophagy in the mutant SOD1 mouse model of amyotrophic lateral sclerosis without slowing disease progression. *Autophagy*. 2018;14:534-551.
117. Rudnick ND, Griffey CJ, Guarnieri P, et al. Distinct roles for motor neuron autophagy early and late in the SOD1(G93A) mouse model of ALS. *Proc Natl Acad Sci U S A*. 2017;114:E8294-E8303.
118. Zhang X, Li L, Chen S, et al. Rapamycin treatment augments motor neuron degeneration in SOD1(G93A) mouse model of amyotrophic lateral sclerosis. *Autophagy*. 2011;7:412-425.
119. Nalbandian A, Llewellyn KJ, Nguyen C, Yazdi PG, Kimonis VE. Rapamycin and chloroquine: the in vitro and in vivo effects of autophagy-modifying drugs show promising results in valosin containing protein multisystem proteinopathy. *PLoS One*. 2015;10:e0122888.
120. Ching JK, Elizabeth SV, Ju JS, Lusk C, Pittman SK, Weihl CC. mTOR dysfunction contributes to vacuolar pathology and weakness in valosin-containing protein associated inclusion body myopathy. *Hum Mol Genet*. 2013;22:1167-1179.
121. Ching JK, Weihl CC. Rapamycin-induced autophagy aggravates pathology and weakness in a mouse model of VCP-associated myopathy. *Autophagy*. 2013;9:799-800.
122. Lilleker JB, Bukhari M, Chinoy H. Rapamycin for inclusion body myositis: targeting non-inflammatory mechanisms. *Rheumatology (Oxford)*. 2019;58:375-376.
123. Castillo K, Nassif M, Valenzuela V, et al. Trehalose delays the progression of amyotrophic lateral sclerosis by enhancing autophagy in motoneurons. *Autophagy*. 2013;9:1308-1320.
124. Patel P, Julien JP, Kriz J. Early-stage treatment with Withaferin a reduces levels of misfolded superoxide dismutase 1 and extends lifespan in a mouse model of amyotrophic lateral sclerosis. *Neurotherapeutics*. 2015;12:217-233.
125. Shintaku J, Guttridge DC. Reining in nuclear factor-kappaB in skeletal muscle disorders. *Curr Opin Clin Nutr Metab Care*. 2013;16:251-257.
126. Schweitzer K, Pralow A. Naumann M. p97/VCP promotes Cullin-RING-ubiquitin-ligase/proteasome-dependent degradation of IkappaBalpha and the preceding liberation of RelA from ubiquitinated IkappaBalpha. *J Cell Mol Med*. 2016;20:58-70.
127. Hammers DW, Sleeper MM, Forbes SC, et al. Disease-modifying effects of orally bioavailable NF-kappaB inhibitors in dystrophin-deficient muscle. *JCI Insight*. 2016;1:e90341.
128. Finanger E, Vandenborne K, Finkel RS, et al. Phase 1 study of Edasalonexent (CAT-1004), an Oral NF-kappaB inhibitor, in pediatric patients with Duchenne muscular dystrophy. *J Neuromuscul Dis*. 2019;6:43-54.

How to cite this article: Korb MK, Kimonis VE, Mozaffar T. Multisystem proteinopathy: Where myopathy and motor neuron disease converge. *Muscle & Nerve*. 2021;63:442–454. https://doi.org/10.1002/mus.27097