Multisystem proteinopathy

Intersecting genetics in muscle, bone, and brain degeneration

J. Paul Taylor, MD, PhD

Correspondence to
Dr. Taylor:
jpaul.taylor@stjude.org

Neurology® 2015;85:658–660

Multisystem proteinopathy (MSP) is an inherited pleiotropic degenerative disorder that can affect muscle, bone, and the nervous system and was first reported as familial motor neuron disease in association with Paget disease of bone (PDB).[1] The MSP phenotype also involves inclusion body myopathy (IBM) or frontotemporal dementia (FTD).[2] The acronym "IBMPFD" describes some families with this syndrome, but it has outlived its usefulness since other phenotypic features sometimes dominate the clinical picture: parkinsonism[3,4] and peripheral neuropathy[5,6] occur, and motor neuron dysfunction is frequent (11 of 17 consecutive MSP cases in one series).[7] An operational definition of MSP is a combination of 2 or more of IBM, PDB, and amyotrophic lateral sclerosis (ALS)/FTD (where ALS and FTD are considered as one spectrum). Histopathologically, MSP-affected tissues have ubiquitin-positive inclusions that contain RNA-binding proteins, such as TDP-43, hnRNPA1, and hnRNPA2B1, but may also include positive staining for proteins that mediate ubiquitin-dependent autophagy, including p62/SQSTM1, VCP, optineurin, and ubiquilin-2.[8–10]

Disease-causing mutations in *VCP* provided the first insight into the molecular etiology of MSP,[11] accounting for up to 50% of families with this genetically heterogeneous syndrome.[12] Mutations in *HNRNPA2B1* and *HNRNPA1* were subsequently identified in families with MSP that was clinically and histopathologically indistinguishable from *VCP* mutation cases.[13] These discoveries prompted recognition that rare pathogenic genetic mutations are lurking in larger populations of patients with more common MSP-related diseases, such as ALS and FTD. For example, mutations in *VCP*, *HNRNPA1*, and *HNRNPA2B1* have been identified in sporadic and familial forms of ALS.[13–15]

In this issue of *Neurology*®, Bucelli et al. report the identification of disease-causing mutations in *SQSTM1* in a family with an autosomal dominant IBM that clinically and histopathologically closely resembles that seen in association with *VCP*, *HNRNPA2B1*, and *HNRNPA1* mutations.[16] The pattern of muscle weakness was that of a distal or facioscapulo distal myopathy, and the muscle pathology demonstrated rimmed vacuoles as well as inclusions of both TDP-43 and SQSTM1. Whole-exome sequencing identified a likely pathogenic c.1165+1G>A splice donor variant in *SQSTM1* in these cases. (Pathogenic mutations in *SQSTM1* are a frequent cause of PDB[17] and are responsible for rare cases of sporadic and familial ALS and FTD.[18,19]) Mutations in *SQSTM1* are now associated with pleiotropic clinical features that include myopathy, dementia, motor neuron disease, and PDB and should, as the authors conclude, be included among the MSPs (table).

Other mutations in functionally related genes are associated with diseases that have clinical and histopathologic features closely related to those caused by mutations in *VCP*, *HNRNPA2B1*, *HNRNPA1*, and *SQSTM1*. For example, mutations in *MATR3*, which encodes an RNA-binding protein that physically associates with TDP-43, hnRNPA1, and hnRNPA2B1, cause a form of inherited distal myopathy[20]; identical mutations in *MATR3* have been associated with familial ALS.[21] Lin et al.[22] reported a case of bulbar-onset ALS in association with an *MATR3* mutation and suggested, after a relevant literature review, that *MATR3*-related disease be included among the MSPs. We have included *MATR3*-related myopathy and motor neuron disease as MSP5 (table). Furthermore, mutations in 2 additional members of the hnRNP family, *HNRNPDL* and *TIA1*, caused 2 related myopathies, subclassified clinically as limb-girdle muscular dystrophy 1G and Welander distal myopathy.[23,24] Whether or not additional neurologic or bone phenotypes are identified in association with *HNRNPDL* and *TIA1*, the functional relationship of these RNA-binding proteins to MSP-associated proteins suggests overlapping molecular pathogenesis.

The genes associated with MSP or related diseases fall into 2 conspicuous categories: RNA-binding proteins and proteins that mediate ubiquitin-dependent

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From the Department of Cell and Molecular Biology, St. Jude Comprehensive Cancer Center, St. Jude Children's Research Hospital, Memphis, TN.

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Table Genes associated with multisystem proteinopathy and closely related disorders

Gene	Function	Syndrome	Associated phenotypes	Disease protein found in inclusions
VCP	Ubiquitin-dependent segregase	Multisystem proteinopathy 1	Myopathy, dementia, motor neuron disease, Paget disease of bone	Yes
HNRNPA2B1	RNA-binding protein	Multisystem proteinopathy 2	Myopathy, dementia, motor neuron disease, Paget disease of bone	Yes
HNRNPA1	RNA-binding protein	Multisystem proteinopathy 3	Myopathy, motor neuron disease, Paget disease of bone	Yes
SQSTM1	Ubiquitin-dependent autophagy	Multisystem proteinopathy 4	Myopathy, dementia, motor neuron disease, Paget disease of bone	Yes
MATR3	RNA-binding protein	Multisystem proteinopathy 5	Myopathy, motor neuron disease	Yes
HNRNPDL	RNA-binding protein	Limb-girdle muscular dystrophy	Myopathy	Yes
TIA1	RNA-binding protein	Distal myopathy	Myopathy	Yes
TARDBP	RNA-binding protein	Amyotrophic lateral sclerosis/frontotemporal dementia	Motor neuron disease, dementia	Yes
FUS	RNA-binding protein	Amyotrophic lateral sclerosis/frontotemporal dementia	Motor neuron disease, dementia	Yes
OPTN	Ubiquitin-dependent autophagy	Amyotrophic lateral sclerosis	Dementia, motor neuron disease, Paget disease of bone[a]	Yes
UBQLN2	Ubiquitin-dependent autophagy	Amyotrophic lateral sclerosis	Motor neuron disease	Yes

[a] *OPTN* has been linked to Paget disease of bone by genome-wide association study, but causative association remains to be established.[33]

autophagy. hnRNPA2B1, hnRNPA1, hnRNPDL, and TIA-1 are all paralogous RNA-binding proteins of the hnRNP family, as are the ALS-/FTD-related proteins TDP-43 and FUS. Disease-causing mutations in these RNA-binding proteins typically reside in a conserved domain found in each protein that mediates the assembly of RNA granules, specialized cytoplasmic RNA protein assemblies that control posttranscriptional messenger RNA metabolism. The consequence of disease mutations is excess assembly and persistence of RNA granules, probably accounting for accumulation of granule components in pathologic inclusions. This disturbance of RNA granule dynamics likely alters RNA metabolism and probably contributes to disease pathogenesis.[25]

VCP is a ubiquitin-dependent segregase that extracts proteins from multimeric complexes and is required for ubiquitin-dependent autophagy,[26] including autophagic degradation of RNA granules; the result of disease mutations in *VCP* is accumulation of persistent RNA granules identical to those caused by mutations in RNA-binding proteins.[27] Thus, failure to degrade RNA granules via autophagy is likely a key contributor to pathogenesis. Consistent with this idea, SQSTM1 is a ubiquitin-dependent autophagic adaptor protein that targets aggregated proteins to the autophagosome.[28] Similarly, 2 other adaptors required for ubiquitin-dependent autophagy, *OPTN* and *UBQLN*, are frequently found in the pathology of MSP and related diseases, and mutations in these 2 genes are causative of ALS and, in the case of *OPTN*, FTD.[29–32]

The phenomenon of MSP raises 2 major questions. First, why do patients with identical mutations in the same gene sometimes develop quite distinct clinical phenotypes affecting different tissues? The existence of modifier genes is an obvious possibility, but the high prevalence of pleiotropy even among closely related family members argues that other stochastic factors, perhaps at the cellular level, may be at work. Second, what can we learn from MSP about the etiologic relationship between seemingly distinct age-related degenerative diseases of muscle, bone, and brain? The current evidence suggests that subsets of patients with ALS, FTD, IBM, and PDB share a common molecular pathogenesis related to the metabolism of RNA granules and their destruction by autophagy. Thus, therapeutic development for restoring RNA granule homeostasis, so-called ribostasis,[25] may apply to a broad spectrum of age-related degenerative diseases.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

J.P. Taylor reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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