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). The MSP phenotype also involves inclusion body myopathy (IBM) or frontotemporal dementia (FTD). 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 and peripheral neuropathy occur, and motor neuron dysfunction is frequent (11 of 17 consecutive MSP cases in one series). 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, hnRNP A1, and hnRNP A2B1, but may also include positive staining for proteins that mediate ubiquitin-dependent autophagy, including p62/SQSTM1, VCP, optineurin, and ubiquilin-2.

Disease-causing mutations in VCP provided the first insight into the molecular etiology of MSP, accounting for up to 50% of families with this genetically heterogeneous syndrome. Mutations in HNRNPA2B1 and HNRNPA1 were subsequently identified in families with MSP that was clinically and histopathologically indistinguishable from VCP mutation cases. 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.

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. 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 and are responsible for rare cases of sporadic and familial ALS and FTD.) 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, hnRNP A1, and hnRNP A2B1, cause a form of inherited distal myopathy, identical mutations in MATR3 have been associated with familial ALS. Lin et al. 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, HNRNPD1 and TIA1, caused 2 related myopathies, subclassified clinically as limb-girdle muscular dystrophy 1G and Wandler distal myopathy. Whether or not additional neurologic or bone phenotypes are identified in association with HNRNPD1 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...
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 UBQLN2, 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.

### Table

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Syndrome</th>
<th>Associated phenotypes</th>
<th>Disease protein found in inclusions</th>
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<td>VCP</td>
<td>Ubiquitin-dependent segregase</td>
<td>Multisystem proteinopathy 1</td>
<td>Myopathy, dementia, motor neuron disease, Paget disease of bone</td>
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<td>HNRNPA2B1</td>
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<td>HNRNPA1</td>
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<td>SQSTM1</td>
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<td>MATR3</td>
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<td>TIA1</td>
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<td>Myopathy</td>
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<td>TARDBP</td>
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<td>FUS</td>
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<td>OPTN</td>
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<td>Amyotrophic lateral sclerosis</td>
<td>Dementia, motor neuron disease, Paget disease of bone*</td>
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<tr>
<td>UBQLN2</td>
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<td>Amyotrophic lateral sclerosis</td>
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</table>

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

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### DISCLOSURE

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

### REFERENCES

1. Tucker WS Jr, Hubbard WH, Stryker TD, et al. A new familial disorder of combined lower motor neuron...


