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Mutations in prion domains of RNA binding proteins hnRNPA2/B and A1 cause IBM associated with Paget's disease, dementia and ALS

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Inclusion body myopathy (IBM) associated with paget's disease of the bone, fronto-temporal dementia and amyotrophic lateral sclerosis (ALS) is a multisystem degenerative proteinopathy (MSP) unified pathologically by ubiquitinated inclusions and TDP-43 accumulation. TDP-43 is an RNA binding protein with a Q/N rich prion-like domain (PrLD). PrLDs in RNA binding proteins mediate the assembly of RNA processing granules. Dominantly inherited mutations in valosin containing protein (VCP) have been previously reported to cause this syndrome. We identified two families with an MSP-like phenotype that did not harbor VCP mutations. Exome sequencing identified identical aspartate to valine mutations in two homologous RNA binding proteins hnRNPA2/B1 and hnRNPA1. These mutations introduce a potent "steric zipper" motif into their PrLD, which accelerates formation of self-seeding fibrils that can cross-seed polymerization of wild-type hnRNP. Disease causing mutations also promote incorporation of hnRNPA2 and A1 into stress granules and drive the formation of cytoplasmic inclusions in animal models. Consistent with this, MSP patient muscle, including VCP-associated MSP, accumulates hnRNPA2/B1, A1 and TDP-43 as sarcoplasmic aggregates that redistribute from their normal nuclear localization. Sporadic inclusion body myositis (sIBM) patient tissue also accumulates hnRNPA2/B1 and A1, as well as TDP-43 aggregates. Other distinctive features in MSP patient muscle biopsies include large regions of myopathic grouping, eosinophilic inclusions and rimmed vacuoles. Dysregulated polymerization of RNA binding proteins with PrLDs is an emerging pathogenic mechanism associated with degenerative phenotypes in IBM, ALS and dementia.

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