Strumpellin is a novel VCP binding protein linking Hereditary Spastic Paraplegia to protein aggregation diseases.

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Mutations of the human VCP gene cause autosomal-dominant inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD). We identified strumpellin as a novel VCP binding partner. Strumpellin mutations have been shown to cause hereditary spastic paraplegia. We demonstrate that strumpellin is a ubiquitously expressed protein present in cytosolic and endoplasmic reticulum cell fractions. Over-expression or ablation of wild-type strumpellin caused significantly reduced wound closure velocities in wound healing assays, whereas over-expression of the disease causing strumpellin N471D mutant showed no functional effect. Strumpellin knock-down experiments in human neuroblastoma cells resulted in a dramatic reduction of axonal outgrowth. Knock-down studies in zebrafish revealed severe cardiac contractile dysfunction, tail curvature and impaired motility. The latter phenotype is due to a loss of central and peripheral motoneuron formation. These data imply a strumpellin loss-of-function pathogenesis in hereditary spastic paraplegia. In the human central nervous system strumpellin shows a pre-synaptic localization. We further identified strumpellin in pathological protein aggregates in IBMPFD and various myofibrillar myopathies. Beyond hereditary spastic paraplegia, our findings imply that mutant forms of strumpellin and VCP may have a concerted pathogenic role in various protein aggregate diseases.