Lysosomal biogenesis defects in HSP with thin corpus callosum

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Autophagy is an intracellular mechanism that cells use to adapt to changes in their environment, coordinating the degradation and recycling of cellular components and organelles to maintain homeostasis. Lysosomes are critical organelles for terminating autophagy via fusion with mature autophagosomes, generating autolysosomes that degrade autophagic materials. Maintenance of the lysosomal population is thus essential for autophagy-dependent cellular clearance. We now demonstrate that the two most common autosomal recessive HSP gene products, the SPG15 protein spastizin and SPG11 protein spatacsin, play pivotal roles in autophagic lysosome reformation (ALR), a pathway generating new lysosomes. Lysosomal targeting of spastizin requires its FYVE (present in Fab1, YOTB, Vac1, and EEA1) domain, which binds phosphatidylinositol 3-phosphate. Furthermore, loss of spastizin or spatacsin results in depletion of free lysosomes (those competent to fuse with autophagosomes) and an accumulation of autolysosomes, reflecting a failure in ALR. Mechanistically, spastizin and spatacsin are essential components for initiation of lysosomal tubulation. These findings uncover a specific link of the autophagy/lysosomal biogenesis machinery to neurodegeneration, with important implications for these common forms of complex HSP.