## Converging mechanisms of SPG-mutated ER shaping proteins in lipid droplet biogenesis

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A number of converging cellular pathologic themes are emerging for the HSPs. The most common forms of HSP - SPG3A, SPG4, and SPG31 – are caused by autosomal dominant mutations in genes that encode proteins that interact with one another and function in shaping and distributing the tubular endoplasmic reticulum (ER) network in cells. However, the specific functions of the ER important for HSP pathogenesis remain unclear. One key role for the tubular ER is in the synthesis, modification, and distribution of lipids, fatty acids and cholesterols throughout the cell. Furthermore, an increasing number of HSP gene products are being identified that participate in lipid, fatty acid, and cholesterol synthesis and modification, and many localize to the ER. We have used a multipronged approach comprising knock-out and knock-in mouse models, CRISPR-derived knock-out cell lines, and transient cell expression studies to investigate the role of the most common HSP gene products in lipid metabolism. We have found a significant effect of the atlastin-1 (mutated in SPG3A) and REEP1 (mutated in SPG31) proteins in the formation of lipid droplets in cells, with some knock-out mouse models showing evidence of lipodystrophy. We are currently using proton MR spectroscopy and imaging modalities such as coherent anti-Stokes Raman scattering microscopy (CARS) to investigate changes in lipids in the central nervous system of these HSP mouse models. The involved metabolic pathways may be particularly amenable to pharmacologic modulation.