Mutations in RNA-binding proteins (RBPs) and in genes regulating autophagy are frequent causes of familial amyotrophic lateral sclerosis (fALS). The P56S mutation in vesicle-associated membrane protein-associated protein B (VAPB) leads to fALS (ALS8) and spinal muscular atrophy (SMA). While VAPB is primarily involved in the unfolded protein response (UPR), vesicular trafficking and in initial steps of the autophagy pathway, the effect of mutant P56S-VAPB on autophagy regulation in connection with RBP homeostasis has not been explored yet. Examining the muscle biopsy of our index ALS8 patient of European origin revealed globular accumulations of VAPB aggregates co-localised with autophagy markers LC3 and p62 in partially atrophic and atrophic muscle fibres. In line with this skin fibroblasts obtained from the same patient showed accumulation of P56S-VAPB aggregates together with LC3 and p62. Detailed investigations of autophagic flux in cell culture models revealed that P56S-VAPB alters both initial and late steps of the autophagy pathway. Accordingly, electron microscopy complemented with live cell imaging highlighted the impaired fusion of accumulated autophagosomes with lysosomes in cells expressing P56S-VAPB. Consistent with these observations, neuropathological studies of brain and spinal cord of P56S-VAPB transgenic mice revealed signs of neurodegeneration associated with altered protein quality control and defective autophagy. Autophagy and RBP homeostasis are interdependent, as demonstrated by the cytoplasmic mis-localisation of several RBPs including pTDP-43, FUS, Matrin 3 which often sequestered with P56S-VAPB aggregates both in cell culture and in the muscle biopsy of the ALS8 patient. Further confirming the notion that aggregation of the RBPs proceeds through the stress granule (SG) pathway, we found persistent G3BP- and TIAR1-positive SGs in P56S-VAPB expressing cells as well as in the ALS8 patient muscle biopsy. We conclude that P56S-VAPB-ALS8 involves a cohesive pathomechanism of aberrant RBP homeostasis together with dysfunctional autophagy. [1)].

1)
Tripathi P, Guo H, Dreser A, Yamoah A, Sechi A, Jesse CM, Katona I, Doukas P, Nikolin S, Ernst S, Aronica E, Glaß H, Hermann A, Steinbusch H, Feller AC, Bergmann M, Jaarsma D, Weis J, Goswami A. Pathomechanisms of ALS8: altered autophagy and defective RNA binding protein (RBP) homeostasis due to the VAPB P56S mutation. Cell Death Dis. 2021 May 10;12(5):466. doi: 10.1038/s41419-021-03710-y. PMID: 33972508.