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Title	Development of new viral-mediated cell models of ALS-linked UBQLN2 pathology
Abstract (max 300w)	Sporadic and familial forms of ALS have been shown to be caused by abnormal patterns of aggregation in a set of cellular proteins including TDP-43 and ubiqulilin2. The UBQLN2 gene encodes a protein that acts through the ubiquitin-proteasome protein pathway to degrade proteins, but mechanisms of this process and changes in disease remain unclear. We aimed to develop a viral mediated human cell model to investigate mechanisms of UBQLN2 pathology in ALS. Lentiviral plasmids, for mRuby2-UBQLN2 (wildtype, and three different disease mutants) and mRuby-2 alone, were introduced to cells alongside lentiviral packaging constructs. Viral supernatants were concentrated and delivered to HEK-293 cells. mRuby2 fluorescence of transduced cultures was used to optimise transduction levels and analyse formation of UQBLN2 inclusions. Protein extracts were prepared and quantitative western blot performed for UBQLN2 protein levels. Similarly transduced cultures immunostained for cellular and autophagy pathway markers by confocal microscopy analysis. UQBLN2 immunoblot confirmed expression of the mRuby2-UBQLN2 protein in both soluble and insoluble fractions of each of the UQBLN2 transduced cultures. mRuby positive puncta were observed in WT and disease associated UBQLN2 localising with known ALS associated proteins, such as TDP-43, and autophagy pathway markers p62, reminiscent of disease pathology We developed a viral-mediated cell model of UBQLN2 expression that provides consistent levels of transduction across experimental replicates generating highly reproducible data. These models will be useful for further studies to elucidate the role of UBQLN2 is ALS, with potential to provide new indicators for disease therapies.

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