Neuronal expression of Ubiquilin-2 mutant exacerbates TDP-43 aggregation in ALS mouse mode

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**Background:** Mutations in the gene encoding Ubiquilin-2 (UBQLN2) are linked to amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). UBQLN2 plays a central role in ubiquitin proteasome system (UPS) and UBQLN2 up-regulation exacerbates TDP-43 cytoplasmic aggregates. **Methods:** To analyse interaction between UBQLN2 and TDP-43 and to produce a relevant ALS animal model, we have generated a new transgenic mouse expressing UBQLN2G348C under the neurofilament heavy (NFH) gene promoter. The mice were then bred with our previously described TDP-43P497H mice to generate double transgenic mice. **Results:** With low expression UBQLN2, the double transgenic mice developed TDP-43 cytosolic accumulations in motor neurons starting at 5 months of age. These double transgenic mice exhibited motor neuron loss, muscle atrophy, as well as motor and cognitive deficits during aging. The microglia from double transgenic mice were hyperresponsive to lipopolysaccharide (LPS). In vivo and in vitro analyses suggested that extra UBQLN2 proteins can exacerbate cytoplasmic TDP-43 accumulations by competing with the UPS for binding to ubiquitin. Thus, increasing the pool of ubiquitin promoted the UPS function with ensuing reduction of TDP-43 aggregation. **Conclusions:** In conclusion, the double transgenic UBQLN2G348C, TDP-43P497H mice provides a unique mouse model of ALS/FTD with enhanced TDP-43 pathology that can be exploited for drug testing.