ALS-associated mutant ubiquilin 2 impairs protein degradation via autophagy-lysosome system

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Ubiquilin 2 (UBQLN2) has ubiquitin-like and ubiquitin-associated domains and regulates protein degradation systems. Missense mutations of UBQLN2 have been recently identified as causal genes of familial amyotrophic lateral sclerosis (ALS). ALS-associated mutant UBQLN2 has been reported to impair protein degradation via ubiquitin-proteasome system. In the present study, we investigated how mutant UBQLN2 affects protein degradation via autophagy-lysosome system, which is classified into three pathways, macroautophagy (MA), microautophagy (mA) and chaperone-mediated autophagy (CMA). We first assessed mA/CMA activity using AD293 cells stably expressing GAPDH-HT, a marker of mA/CMA activity. Overexpressed wild-type UBQLN2 decreased mA/CMA activity, and the overexpression of mutant UBQLN2 exacerbated the decrease of mA/CMA activity. Experiments using rapamycin and mycophenolic acid, activators of mA and CMA, respectively, revealed that CMA was mainly impaired by wild-type and mutant UBQLN2. As for MA, autophagic flux assay using bafilomycin A1, a lysosome inhibitor, revealed that mutant UBQLN2 decreased MA activity in AD293 cells. These findings suggest that ALS-associated mutant UBQLN2 impairs MA and CMA and disturbs protein quality control. This disturbance would be related to the pathogenesis of ALS caused by UBQLN2 mutation.