OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-21-00451
Title: Ubiquitin homeostasis disruption, a common cause of proteostasis collapse in ALS?
Reviewer's Name: Fuminori Tokunaga
Reviewer's country: Japan

COMMENTS TO AUTHORS

ALS is a neurodegenerative disease with a poor prognosis, and the development of treatment for it is an urgent need for humankind. In this manuscript, the authors outlined the contribution of the ubiquitin system to the ALS proteinopathy, and suggested that recovery of free ubiquitin amount will be an extremely important therapeutic target by mainly introducing two important papers (Farrawell NE et al. JCS 2018 and iScience 2020).

Minor comments:

1. On page 2, line 13; The authors described for the polyubiquitination through seven Lys residues, but now a variety of ubiquitination, such as linear ubiquitination via the N-terminal Met1, complex types of branched and hybrid chains, and posttranslational modification of ubiquitin (phosphorylation and acetylation) are identified. I would like you to briefly touch that this "ubiquitin code" plays an important role in the various cellular functions, and also found in inclusions of ALS. In addition, the ubiquitin system plays an important role in neuroinflammation through innate immune responses, such as NF-κB and interferon production pathways, and gut microbiota-mediated chronic inflammation is an important target in ALS treatment. I would like you to briefly introduce this point as well.
2. On page 2, line 42; DUBs are important for regulating the amount of free ubiquitin, so please briefly explain the number of genes and catalytic mechanism in human cells.