OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-22-01349
Title: Etiology matters - genetic and acquired prion diseases engage different mechanisms at a presymptomatic stage
Reviewer's Name: Elena De Cecco
Reviewer's country: Switzerland

COMMENTS TO AUTHORS

This Perspective has a clear and logical organization. The choice of the two papers to describe in more detail is appropriate and clearly highlights the differences between existing models for prion diseases. I have some minor suggestions that in my opinion would improve the manuscript:
- Page 1 (line 46): "PrP is also a strange beast" - I would recommend the authors to use a more scientific and professional language.
- Page 2 (line 32): D178N mutation is linked to both FFI and gCJD. What determines the type of pathology is the genotype at the codon 129: M haplotype causes FFI, while V haplotype causes gCJD. Modify the text accordingly.
- Page 6: which pathways do the DEGs in the FFI and gCJD models belong to?
- Page 7 (lines 10-13): this idea is interesting and I would suggest the authors to comment a bit more on this.
- Since you talk about prion diseases, you should include at least the first papers that described prions (Prudiner 1982; Bueler and Aguzzi, 1993; Brandner 1996).