OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
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Title: Synaptopathy in CHMP2B frontotemporal dementia highlights the synaptic vesicle cycle as a therapeutic target in frontotemporal dementia/amyotrophic lateral sclerosis
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COMMENTS TO AUTHORS

This short perspective article evaluates the literature-based evidence to support the potential of the synaptic vesicle (SV) cycle as an early and targetable pathway for therapeutic intervention in FTD/ALS. They focus primarily on CHMP2B transgenic mice model as an example to showcase the importance of SV cycle as a convergent pathology in FTD/ALS.

Overall, this is a short review and is interesting. It highlights SV cycle that can be studied to advance FTD/ALS pathogenesis. However, the conclusions are not fully supported and somewhat difficult to reconcile. A series of questions remain open, and the article would profit from additional information or at least from more focused discussion of these points:

1. If deemed adequate, the authors could also add a short paragraph indicating where (i.e., in which neuronal/glial populations) are some of the FTD/ALS genes discussed are expressed? This would be useful for a thoughtful explanation on whether the changes induced by these are cell-autonomous or not on SV cycle.
2. Similarly, it would be adequate, for the non-specialist reader, that the article also highlights different potential mechanisms of SV cycling steps.
3. For the CHMP2B, it could be useful to add on what proportion of FTD/ALS cases have the mutation instead of writing "minor proportion".
4. It would be as well adequate to potentially include a reflection on the other ESCRT-III partners such as CHMP7, and why these may not show enough compensatory power?
5. The authors included a nice scheme on the multiple FTD/ALS associated proteins converge at the synaptic vesicle cycle. In this sense, it would be adequate to discuss what initiates this whole cascade, to refine and find new therapeutic opportunities for intervention, perhaps even earlier on.
6. Despite they may be out of scope, could the authors offer some hint on the potential changes of SV biology in age-related cerebral changes in control cases?
7. On many occasions, some concepts are just stated with little explanation and/or no support literature. Please, include some additional references.
8. For the C9orf72 gene, the authors highlighted the evidence based on zebrafish model. Is there no evidence from other C9 studies using mice model?
9. It will be nice to discuss how different model systems (e.g., iPS cells) can be used for these studies that could highlight the importance of SV cycle in those. The defect in SV cycle described in different culture neurons in those studies with the defects observed in vivo. Are they caused by the same mechanism?