OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00485
Title: Phenotypic heterogeneity in amyotrophic lateral sclerosis type 8 and modifying mechanisms of neurodegeneration
Reviewer's Name: Abhisek Mukherjee
Reviewer's country: USA

COMMENTS TO AUTHORS
In the current manuscript titled "Phenotypic heterogeneity in Amyotrophic Lateral Sclerosis and modifying mechanisms of neurodegeneration" the author presented a perspective about the clinical heterogeneity within ALS8 and our current understanding about the molecular basis. Although it is a timely and interesting topic, I would like to recommend the following changes before consideration for publication.

1. The manuscript appears to be a summary of the work published by Oliveira et al., 2020. In order to represent a general perspective on the topic, I recommend the following.

A. Please discuss the relevance of current work done by other groups in relation to the current topic. Some examples include...

Network analyses reveal novel aspects of ALS pathogenesis
Mario Sanhueza, Andrea Chai, Colin Smith, Brett A McCray, T Ian Simpson, J Paul Taylor, Giuseppa Pennetta. PLoS Genet. 2015 Mar 31;11(3):e1005107.

Nucleocytoplasmic transport defect in a North American patient with ALS8. Robert D Guber , Alice B Schindler, Maher S Budron, Ke-Lian Chen, Yuebing Li, Kenneth H Fischbeck, Christopher Grunseich. Ann Clin Transl Neurol. 2018 Feb 4;5(3):369-375.

VAPB/ALS8 interacts with FFAT-like proteins including the p97 cofactor FAF1 and the ASNA1 ATPase. Yorann Baron, Patrick G Pedrioli, Kshitiz Tyagi, Clare Johnson, Nicola T Wood, Daniel Fountaine, Melanie Wightman, Gabriela Alexandru. BMC Biol. 2014 May 29;12:39.

Amyotrophic lateral sclerosis-related VAPB P56S mutation differentially affects the function and survival of corticospinal and spinal motor neurons. Leonardo Aliaga, Chen Lai, Jia Yu, Nikolai Chub, Hoon Shim, Lixin Sun, Chengsong Xie, Wan-Jou Yang, Xian Lin, Michael J O'Donovan, Huaibin Cai. Hum Mol Genet. 2013 Nov 1;22(21):4293-305.

B. Please briefly talk about the other mutations noted in VABP (T46I, V260I) in ALS8.

C. Please briefly mention about the function of VABP and what we know about the role of these mutations in on VABP in associate with ALS.

2. The manuscript does not discuss about the phenotypic heterogeneity in amyotrophic lateral sclerosis in general. It only focuses on ALS8. I would recommend changing the title accordingly.

3. In the figure, the author is trying to show that cell death, mitochondrial activity, energetic metabolism are significantly compromised in sever ALS8 compared to mild ALS8. However, in the current form, the figure suggests that these function are improved in mild ALS8. Please correct it.