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Peer Review

Review of: "VPS13D Mutations Affect Mitochondrial Homeostasis and Locomotion in Caenorhabditis elegans"

Hyun Sung[1]

1. Department of Pharmacology, School of Medicine, Pusan National University, Korea, Republic of

Wang et al. utilized *C. elegans vps-13D* mutant animals, including two deletion mutants and three pathogenic missense mutants, to investigate the role of VPS13D in SCAR4 pathogenesis. The authors conducted animal locomotion assays and mitochondrial validations to gain insights into the cellular mechanisms underlying behavioral defects. Through intracellular mitochondrial analyses, they showed that *vps-13D* mutations alter mitochondrial structure and induce mitochondrial UPS. Prior to this study, using the *Drosophila* model, this group had elegantly demonstrated that VPS13D affects mitochondrial morphology and mitophagy by regulating mitochondria-ER contact sites (Shen et al., Curr Biol. 2021). In this study, the authors introduce a new *C. elegans* model, further verifying the impact of VPS13D on mitochondrial morphology and expanding research into *vps13D*-associated SCAR4 pathogenesis.

Major comments:

(1) Unlike the *vps-13D* deletion mutants, the pathogenic missense mutants, particularly *vps-13D(N2454S)*, do not seem to display prominent defects in animal behavior, including locomotion. Considering the results from the mitochondrial morphology analysis and mitochondrial homeostasis validation, what could be the key underlying cellular mechanisms in SCAR4-associated pathogenesis? Are the pathological phenomena more likely to depend on the induced mitochondrial UPR rather than the disrupted mitochondrial morphology? Are there any differences in vps-13D mRNA levels between the deletion and missense mutants?

(2) Since mutations in vps-13D impact mitochondrial homeostasis by inducing the mitochondrial UPR, it would be worth testing the mechanisms of autophagy, particularly mitophagy, in this animal system. It would be interesting to examine mitochondrial membrane potential or observe the autophagosomal

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engulfment process in these mutant worms. Additionally, it would be valuable to investigate ER-phagy as well.

Minor comments:

(1) In Figure 2D, it would be helpful to include representative worm track images from the three missense mutants, even if there are no differences compared to the WT.

(2) In Figure 5, is it possible that the *vps-13D* mutant worms could have elevated FZO-1 levels, similar to what was observed in the fly model?

Declarations

Potential competing interests: No potential competing interests to declare.