OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-22-00491
Title: LncRNA H19 Regulates Nerve Degeneration and Regeneration by Activating SEMA 6D in Injured Rat Peripheral Nerves
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COMMENTS TO AUTHORS

This manuscript explored the role of LncRNA H19 on axon injury mechanism by using AAV to manipulate the H19 expression using the rat sciatic nerve injury model. The authors reported that LncRNA H19 may regulate peripheral nerve degeneration by activating SEMA 6D in injured nerves. Although the result and conclusion of this manuscript sound promising, the manuscript still lacks some clarification of the presented results. The list of comments are listed below.

- Please use the full word of SNI before introducing the abbreviation in line 43.
- How long is the Wallerian degeneration (WD) in the rat sciatic nerve injury model? When will this event begin after the onset of injury? What was the rationale behind the selection of the analyzed timepoint?
- Figure 1 is quite blurred making it difficult to see the staining. Please re-check the resolution quality of the figures.
- Please specify number of total RNA concentration used for RT-qPCR
- Where are the result figures of section 3.2 and 3.3?
- How many rats were used in each group of the experiment? Please also specify the sample number in all the graphs presented.
- In section 2.1, please describe more about the 4 animal groups as well as the NC-sh and NC-p group. Were they the same group of negative controls?
- Please specify in section 3.5 whether it was proximal or distal nerve stump that the authors analyzed in the experiment.
- Figure 3 and the scale bars are quite blurred. Please adjust the figures. The reviewer suggests the author to add a quantitative data to support the difference in the fluorescence intensity of beta-tubulin III of the two groups. Which position (middle, near proximal/distal stump) of the enlarged photos in Figure 3C were taken from the whole nerve section?
- In figure 3, the AAV positive green fluorescent signals were not that strong, where in section 3.2, the authors mentioned a high expression of AAV in DRG axons. Please explain.
- The authors showed data related to the effect of overexpression of H19 on axonal growth. It would be great if the effect of the interference of H19 was also included.
- In figure 5 and figure 6, why were there quite a large difference in the negative control group between NC-sh and NC-p? For example, at week 2, the average SFI value of NC-sh was around -93, whereas that of NC-p was around -87. Also, at week 4, the pain response time of NC-sh was around 20 s, while the NC-p group was just 10 s which showed a large variation in the control groups. This might effect the interpretation of the statistical analysis of the results. Please explain.
- In the discussion line 57, please cite the previous research.
- According to the result presented, overexpression of H19 inhibited axonal growth but at the same time promoted formation of new myelin sheath. How is this possible? Please discuss.