Author’s response to reviews

Title: A Novel Mutation in SEPN1 Causing Rigid Spine Muscular Dystrophy 1: A Case Report

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Author’s response to reviews:

Dear Editor,

Thank you very much for considering our manuscript for publication in BMC medical genetics. We revised the manuscript according to the reviewers’ comments. In the resubmitted revision point to point responses to every point raised by the reviewers with reference to the page and line numbers in the manuscript are provided. I hope you will find the revised version acceptable for publication in your prestigious journal.

Authors’ response to the comments:

1. “The majority of the text concerns general issues not specifically related to the subject. No effort is done in order to comment on whether this subject with a presumed pathogenic novel
SEPN1 variant differs from previously reported SEPN1 phenotypes. Taken together no additional information is given than could be retracted from a mutation database.”

Complied. Changes were made to the text. Further information on clinical and para-clinical evaluations was added to the manuscript (Page 4, Lines 1-4 and Lines 6-14 and Lines 18-19 as highlighted in the manuscript).

2. “In this study, please illustrate the clinical details in more comprehensive and detailed way. Please give the clinical details for the other family members.”

Complied. Further information on clinical and para-clinical evaluations was added to the manuscript (Page 4 Lines 1-4 and Lines 6-14 and Lines 18-19 as highlighted in the manuscript). No other family member was affected (Page 4, Line 3).

3. “In this study, please describe the methodology for identifying the mutation? Please give us the detailed process and quality control system for identifying the candidate variants.”

Further details on WES were provided (Page 4, Line 24-25 as highlighted in the manuscript).

4. “The variant has been written according to the HGVS nomenclature rules. Please check and confirm it.”

The variant was checked and confirmed (Page 5, Line 2 as highlighted in the manuscript).

5. “Please do a functional study of this identified mutation. It is a missense VUS, so functional characterization is required to confirm the pathogenicity. Please do a functional analysis of this mutation by in vitro or in vivo experiments and confirm how this mutation causes the disease.”

Unfortunately, performing an experimental study to evaluate the effects of this variant was not possible due to limited budget. However, as mentioned in the manuscript, the results of the bioinformatics analysis were all supportive of the pathogenicity of the variant. Multiple sequence alignment revealed that the serine residue is conserved across different species. Furthermore, the presence of the mutation in the homozygous form in the affected individual in the family and heterozygous form in other unaffected family members supports the pathogenic role of this variant.
6. “There are some typos and grammar mistakes in the text and need some editorial improvement.”
Corrected. (These minor changes were documented using “Track Changes” in the revised version)

7. “Please, delete irrelevant "general" phrases and sentences.”
The general phrases were deleted (Page 2, abstract, conclusion and Page 7, Last paragraph).

8. “List up and explain all the abbreviation used in this manuscript (SCC, CHH, RJH).”
Done (Page 8, Abbreviations as highlighted).

9. “Overall written English need to improve.”
Done. (These minor changes were documented using “Track Changes” in the revised version)

Thank you again for the careful review and suggestive comments.

Sincerely, Seyed Alireza Dastgheib, MD, MPH, PhD on behalf of all authors