Reviewer's report

Title: Identification of a rare SEPT9 variant in a family with autosomal dominant Charcot-Marie-Tooth disease

Version: 0 Date: 01 Dec 2019

Reviewer: Emanuele Agolini

Reviewer's report:

Thank you for allowing me to review this research article. The manuscript by Grosse et al. entitled 'Identification of a rare SEPT9 variant in a German family with autosomal dominant Charcot-Marie-Tooth disease and cognitive deficits' documents a family with 4 individuals affected by an AD form of CMT disease. In the available affected members, the authors found a missense variant in SEPT9, a gene previously linked to hereditary neuralgic amyotrophy. They suggest SEPT9 as new sufficient candidate gene in CMT. The article is well written but I have some concerns with the current manuscript.

1) In the introduction the authors should specify that they found a missense variant in SEPT9 gene providing some information on its function.

2) In the discussion it would be useful to expand the part on SEPT9 giving more information on the protein, its function, the family to which it belongs, the expression profile and cellular processes in which septins are involved.

3) The authors should perform trio exome sequencing for two important reasons: a) to exclude other variants associated with the cognitive impairment in this family especially in the subject III.4 b) to exclude variants in cancer predisposition genes. In effect, even if SEPT9 plays a role in the development of some types of cancer, germline variants have never been reported in association with cancer-prone syndromes, to my knowledge.

4) Authors should provide the CADD score of the identified variant

5) Authors should provide in the main text the classification of the variant and the criteria used for the classification according to the ACMG guidelines

6) It would be useful to add the molecular modelling study to show the effect of the missense variant on the protein

7) Authors should provide Sanger sequencing figure of the variant.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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