**Author's response to reviews**

**Title:** Evaluation of the endoplasmic reticulum-stress response in eIF2B-mutated lymphocytes and lymphoblasts from CACH/VWM patients

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**Author's response to reviews:** see over
We received the second peer review and comments from you and the referees concerning our manuscript MS 3890058723767528:

**Evaluation of the endoplasmic reticulum-stress response in eIF2B-mutated lymphocytes and lymphoblasts from CACH/VWM patients**

Laetitia Horzinski, Liraz Kantor, Aurélie Huygue, Raphael Schiffmann, Orna Elroy-Stein, Odile Boespflug-Tanguy, Anne Fogli

We thank you and the experts for these comments. Please find below our point-by-point responses to the editor and to the reviewers. We also join the revised manuscript with all new changes made in red colour.

**A) Responses to the Editor**

- As suggested by the Editor, we add in the Table 1 legend the phrasing “Table adapted from Horzinski et al. [16]”
- We also made sure that the correct references were used. Thus, we corrected some reference numbers and we added the new references [5] and [22] in the discussion (see point 1 from responses to reviewers 1 and 2). We effectively replace the reference [15] in the Table 1 legend by the reference [16].

**B) Responses to Reviewer #1 (Graham Pavitt)**

1) In response to the recommendations of reviewers 1 and 2, we added a possible explanation for the differences we observed between PL and EIL in the discussion section. We added the reference [22] (Balachandran and Barber, 2004) in order to discuss this point. The authors of this paper found that immortalization of mouse fibroblasts affected the ability of increased eIF2 phosphorylation to decrease eIF2B activity. They found that cells transformation leads to increased eIF2B expression and therefore to increased GEF activity and to reduced sensitivity to eIF2 phosphorylation. As suggested by reviewer #1,
we could then hypothesize that eIF2B expression is increased in EIL in comparison to PL. This increased eIF2B expression would make the GEF assay more robust in EIL than in PL and would permit to discern more easily differences in activity between normal and eIF2B-mutated patients. This increased eIF2B expression may also make EIL less sensitive to increased eIF2 phosphorylation following the UPR in comparison to PL. [22]

2) As suggested by the reviewer, we added the ELA grant number in the Acknowledgements section.

C) **Reviewer #2 (Mark Peter Ashe)**
In response to the recommendation of the reviewer that an explanation must be given for the data in the discussion, see point 1 in the responses to Reviewer #1 above.

D) **Reviewer #3 (Scot R Kimball)**
1) As suggested by the reviewer, we replaced “nucleotide guanine exchange” with “guanine nucleotide exchange factor” in the first sentence of the Background section.

2) We corrected the typographical error “Fourteen” in the first sentence of the Methods section.

We hope that this revised manuscript will be suitable for publication in the BMC Neurology journal.

Sincerely yours,

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