Reviewer's report

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

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Reviewer: Mark Peter Ashe

Reviewer's report:

The paper describes an investigation of 12 eIF2B-mutated transformed lymphocyte cell lines. The main conclusions from the paper are that eIF2B GEF activity has decreased, and that although this is normally associated with a constitutive level of ER stress response, in these cell lines no difference is observed in this stress response. This was judged by measuring the induction of ATF4 and assessing the activation of downstream genes. On the whole the paper provides new information which will be useful to the field as a whole. However, much of the interpretation is based data not shown and as the results are quite sparse and most of these experiments should be directly presented.

Major compulsory revisions

1. The authors have a previous paper in the PLOS one journal which details GEF measurements of transformed lymphocyte eIF2B mutant lines. I'm not sure what the relationship is between the data in this previously published paper and table I of this manuscript. If the data are presented previously then this should be more implicitly stated. If they are new data then a few examples of the guanine nucleotide exchange rate analyses should be presented.

2. The authors state that translation was inhibited equally in the mutant cell lines relative to controls. They state that 35S-Methionine incorporation assays and polysome analyses from the basis of this conclusion, yet these data are not shown. The primary data from these analyses need to be presented.

3. The authors provide no hypothesis to explain how a cell can have reduced eIF2B activity and yet mounts a normal ER stress response. They should add their thoughts on this into the discussion.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests