Mutations in the protein synthesis factor eIF2B cause a fatal inherited brain disorder. eIF2B enhances nucleotide (GDP) exchange on its partner protein in all cells and is regulated by ER stress agents in many cell types. An eIF2B activity assay using transformed lymphocytes has been established as a biochemical diagnostic for this condition to supplement genetic diagnosis and MRI. It was shown previously by these authors that primary fibroblasts from certain eIF2B patients also exhibit a heightened ER stress response, while it was not possible to monitor a decrease in eIF2B activity in these cells. Identifying simple diagnostic markers for these rare genetic conditions will be useful to speed diagnosis of affected patients.

Here the authors have used the EBV-transformed lymphocyte cell model to assess whether heightened ER stress is also observed in these cells. Unexpectedly, they find that the cells tested respond equally to ER stress agent as do normal control samples. Therefore monitoring ER stress response in these cells is not a useful model/ tool. Thus primary fibroblasts are a useful cell system to monitor the stress response, but not directly measure an eIF2B activity defect, while transformed lymphocytes are useful to measure eIF2B activity, but do not have a heightened stress response.

Taken together these studies highlight our incomplete understanding of the control of the ER stress response in different cell types and so these observations will be useful to a small number of clinical labs developing and using tests for this eIF2B disease. While no explanation for the difference is noted or offered, the ER stress response is widely studied and these results may prompt others to investigate further the underlying mechanism.

Major Compulsory Revisions

1. Figure 2 presents a summary of RT-PCR data in a form that is not easy to understand/ interpret. If I understand it correctly, The primary data for each transcript are normalized to beta2M. Then a ratio between ER stress and non stress is obtained. Then a second ratio is made between data from primary and transformed lymphocytes. Thus the figure represents a ratio of a ratio of normalized data. It would seem more simple and appropriate to present the data for primary and transformed cells separately, in a manner similar to shown in Figure 1. As presented it is impossible to interpret this experiment.
2. Table 1 reports patient data and GEF activity. Much (or all?) of this data was published by the authors recently Horzinski et al PLOS 1, December 2009. Where data has been published before the source should be cited. Depending on the extent of repetition, it may be appropriate to reduce the amount of information presented here, or obtain permission to reproduce it. However it is useful to have at least the correlation between the patient number, protein amino acid changes and GEF activity, to enable the ER stress data to be easily evaluated.

Minor Essential Revisions

1. On page 9 it is stated that the effect of ER stress on incorporation of labelled amino acids was measured, but that the data is not shown. It would be appropriate to present at least the mean data ± SD for control and patent samples, perhaps as a single sentence to illustrate the point more quantitatively.

2. The choice of some abbreviations used seem non obvious. Why 'LLB' for EBV immortalised lymphocytes. Why not 'EIL'? Why 'LP' rather than 'PL' for primary lymphocytes?

3. The word 'proteic' is used frequently presumably in place of protein?

4. Use DNA rather than ADN in Table 1. Perhaps also place DNA and protein changes in different columns.

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