Reviewer's report

Title: Novel loss-of-function PRRT2 mutation causes paroxysmal kinesigenic dyskinesia in a Han Chinese family

Version: 1 Date: 9 April 2014

Reviewer: Peter Hedera

Reviewer's report:

The authors report another disease causing mutation in the PRRT2 gene in a small pedigree with PKD. The detected mutation is another example of SNindels (single nucleotide insertions or deletions) that are so typical for this gene. The predicted product would be a 132 aa truncated protein.

The reported mutation is very similar to other known mutations (simple point mutations are very rare) and it has been postulated before that this is a loss of function (haploinsufficiency). Aberrant localization of truncated proteins was demonstrated in the original paper by Chen et al (their Figure 4) and they saw a cytosolic (instead of membrane) localization of truncated protein.

In this report the predicted protein was shorter and they saw the nuclear expression.

Do the authors think that the difference is in the length of truncated protein?

I think that haploinsufficiency is not disputed. However, what remains unknown is whether under normal conditions the aberrant transcript is the target of nonsense mediated decay or not. The overexpression of cDNA is obviously very artificial and the detection of abnormal protein may be an artifact of overexpression.

The second paragraph of their paper states: "However, no experiments have investigated the pathogenic mechanism of haploinsufficiency or gain-of-function". Again, this is not true and they need to compare their data with the seminal paper by Chen et al.

Overall, the report is competent but does not much what we already know. Furthermore, the authors need to discuss these issues and modify their conclusions.

Major compulsory revision:
1. Compare their expression data with previous work (Chen et al., their figure 4)
2. Discuss overexpression and possible nonsense mediated decay

Minor:
None

Discretionary Revisions
Analysis of mRNA and expressed protein form their patients (given the
expression patterns of PRRT2, this would require iPSC) and this may not be possible and achievable for the authors

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

Quality of written English: Acceptable

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