Reviewer’s report

Title: Broadening the phenotype of the TWNK gene associated Perrault syndrome

Version: 0 Date: 27 Sep 2019

Reviewer: Diana Cornejo

Reviewer's report:

Background
In the first paragraph, precision should be made that the gene is not located in the mitochondria but in the nuclear genome (chromosome 10). However the protein product does act in the mitochondria.
Attention should be made throughout the manuscript regarding the acronyms that should be explicitly mentioned before appearing in the text.
A reference should be added in this part "In ad-PEO3, mild cortical atrophy and white matter abnormalities in subcortical and periventricular regions were described."

Subjects and methods
POLG1 gene was Sanger sequenced, however there is no information in the background that could explain why this gene was analyzed
It is not clear to me why hg18 was used, since there is a more complete human genome version such as hg19 or the later hg38
It would be interesting to give an annex table indicating the 53 genes that conform the used panel
Indicate which was the pipeline used to filter and analyze the sequence data, and as a recommendation variant classification should follow the ACMG guidelines for pathogenicity
Specify which members of the family underwent Sanger screening for the mutations. Where the siblings also tested?
FATHMN, is FATHMM just correct the typo

Case presentation
I think is useful to see the pedigree information with segregation information and Sanger traces of the identified mutations
Denote the transcript used to annotate the mutations as well as the corresponding protein change.
Where the mutations screened in the unaffected siblings?
What is the frequency of the mutations in the ethnic-matched population?

Discussion
I think this paper adds important information about the phenotypic spectrum of this rare disease with clinical, imaging and neuropathological characterization.
I only advise careful interpretation of likely pathogenic mutations based on the ACMG guidelines.
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.

No

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

Yes

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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