Reviewer’s report

Title: Identification of gene mutations in patients with primary periodic paralysis using targeted next-generation sequencing

Version: 2 Date: 15 Nov 2018

Reviewer: Masanori Takahashi

Reviewer’s report:

I think the authors seriously tried to respond most of the reviewer's criticism.

However I feel the rationale to describe the OPA1 mutation (Ala357Thr) among many variants with uncertain significance (VUS) is still lacking. As shown in Figure 1 newly provided in the rebuttal letter, there were many VUS in myopathy-related 245 genes. As is the case with NGS, there were also VUS in other ion channel-related genes including ATP2A1 and KCNJ16 genes. Mutations of the ATP2A1 gene is known to be responsible for Brody myopathy, characterized by exercise-induced impairment of skeletal muscle relaxation and painless cramp. On the other hand KIR5.1 protein encoded by the KCNJ16 is reported to negatively control the activity of Kir2.1 channel encoded KCNJ2 gene, mutations of which cause Andersen-Tawil syndrome, a form of periodic paralysis as found in some patients of this study. Thus it seems very odd to just point out only one VUS of OPA1 and discard all other possibly important VUS.

I think authors should provide more concrete evidence supporting the pathogenicity of OPA1, otherwise it seems inappropriate to describe in the result, to include in the "5 genes" and to list in table 1 and Figure 4.

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.

Yes

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

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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