Reviewer’s report

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

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Reviewer: Masanori Takahashi

Reviewer’s report:

Luo et al. employed targeted next generation sequencing to reveal genetic cause of primary periodic paralysis in Chinese cohort. They identified several interesting variants such as in OPA1 or several novel ones in SCN4A. Thus the study is potentially important but the manuscript simply describes the mutations. The manuscript would clearly benefit from some functional work.

Major

The approach of variant analysis and verification is not clear to me.

Did authors looked for mutations in 245 other genes, only if no mutation in 10 channel genes was identified? How these 10 genes were selected? Is ALG13 gene channel-related? I think there might be high possibility to find pathogenic or novel mutations in the 245 genes, if analyzed, but there is no mention. In my experience, novel mutations with unknown significance can be often encountered in large genes such as RYR1 and TTN.

The pathogenicity of the novel mutations are inconclusive.

The pathogenicity of the novel mutations should be investigated by co-segregation in the family, frequency of in the same ethnic cohort, and some functional analyses.

The authors mentioned segregation analysis but for which sample? If performed for unreported novel mutations, it should be clearly stated. The authors should also provide data showing that the novel mutations identified are not present in their normal ethnic population. I have not fully checked but found existence of several variants in Asian population in ExAC database. In case of Ala1765Thr in SCN4A, the variant is present 64 in 16490 South Asian alleles.

I think mutation in OPA1 is of interest but some functional study is necessary to establish its pathogenicity.

Minor

Abstracts
Many will read only the abstract and simply believe the listed mutations as pathogenic. Thus I think the detailed information of the novel mutations should not be listed in the abstract, unless their pathogenicity was evident.

Methods

Authors stated about the analysis of CNV and RNA in muscle but there is no mention in the results.

References

There are many references which are miss-numbered. Authors should cite original reference for the reported mutations, especially for minor mutation such as Arg1451Leu in SCN4A.

Discussion

Discussion should be shortened. Repetition of the description already appeared in the results should be avoided.

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