Author’s response to reviews

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

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Reviewer reports:

Masanori Takahashi (Reviewer 1): 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.

Response: Thanks for the constructive suggestions. We agree that more concrete evidence supporting the pathogenicity of OPA1 is still insufficient. Functional study is necessary to establish its pathogenicity. Since the patients recruited in this study had primary periodic paralysis (PP), we focus on the known genes of primary PP, there are no other exonic variants of the known genes of primary PP after filtering in the public databases (1000Genome, ESP6500 etc) besides the OPA1 mutation (Ala357Thr). So we try to discuss the pathogenicity of OPA1. But ignoring of other VUS mutations may be not so reasonable. More research will be conducted, but it may take long time to figure out its mechanism. It is appropriate to remove the OPA1 mutation.

We sincerely appreciated all your effort for making this manuscript better.

Chongbo Zhao