Reviewer's report

Title: The role of CACN1AS in predisposition to malignant hyperthermia

Version: 1 Date: 11 August 2009

Reviewer: Nyamkhishig Sambuughin

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Essential points:

1. One of the major limitation of this work is lack of functional data to potentiate involvement of novel Arg174Trp variant in association with MHS. In the absence of functional data, the authors screened 100 control individuals to prove association of Arg174Trp with MHS phenotype. The problem with this data is that a control population of 100 individuals is powered to detect relatively common variants that are more frequent than that of the most frequent mutations in a rare genetic disorder such as MH. In the absence of functional analysis and inadequate numbers of control screened, observations made with Arg174Trp variant could merely be co-incidental. It is advisable to increase number of controls up to 200-250.

2. The phenotype and genotype relationship in MHS especially in MHE individuals is difficult to determine. Substantial numbers of MHE individuals do not carry MH familial mutation. Of 50 clinically MHS individuals enrolled in this study, 20 were diagnosed as MHE by the IVCT test. This needs further comments in discussion.

3. Two novel non-synonomous changes, Gly258Asp and Ser606Asn, found in this study appear to be polymorphisms based on discordance of these variants with MH phenotypes within families (page 10). However, it is not clear from the text how these variants were segregated within families. Due to the lack of these variants in the controls and potential importance for the protein function based on location, it would be important to provide more detailed information on these families.

Minor corrections:

1. Page 13. Consider rewording the last sentence in the first paragraph. Use "numerous or numbers of relatively rare haplotypes" instead of "a lot of relatively rare haplotypes".

2. Page 16. The second sentence from top is not clear. What are implications of allelic heterogeneity of CACNA1S to EC coupling in skeletal and cardiac muscle?

3. Was there any compound heterozygosity with two different rare non-synonymous changes in CACNA1S among 50 MHS subjects enrolled in this study?

4. Recently CACNA1S Arg897Ser variant was found in subjects with
hypokalaemic periodic paralysis (Chabrier S et al., 2008). Suggest adding this variant into table 2.

**Level of interest:** An article of importance in its field

**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.