Reviewer’s report

Title: The role of CACN1AS in predisposition to malignant hyperthermia

Version: 1 Date: 10 July 2009

Reviewer: Pia Bernasconi

Reviewer’s report:

The Authors have performed a well-done and extensive analysis of CACNA1S gene with regard to its role in predisposition to malignant hyperthermia. They have found only one potentially pathogenetic change in CACNA1S gene, which is now important to check in patients negative for the common RyR1 mutations. Moreover, this finding supports the interpretation that in RyR1 negative patients other loci need to be analyzed in order to get a more comprehensive view of these patients. Nevertheless since only one mutation has been found it should be kept in mind that overall mutations in the CACNA1S gene do not seem to play a major role in influencing the excitation contraction process. In this regard I would advice to add to the title of the manuscript a reference indicating that CACNA1S gene does not seem so crucial in MH.

Minor essential revisions are:

The Authors should be consistent throughout the manuscript since sometimes they wrote 50 independent MH families sometimes 50 MH patients and this is confounding to the reader.

In Materials and Methods, Samples Section Author are referring to 50 independent UK susceptible samples but in the description of this cohort of patients they are referring to 33 males and 21 females and this looks like incorrect numbers. Authors should explain this difference.

No information has been provided with regard to the availability of the informed consent from individuals included in the present study. Authors should specify whether they have had patients’ permission.

In Results, CACNA1S sequencing section, the Author should specify whether the number in parentheses near the amino acid position [e.g. 69 (n=4)] is referring to the number of MH patients with that specific mutation. Furthermore, the number reported in the text is sometimes different from that reported in Table 2 where, if the reviewer understands correctly, also the healthy donors are reported. The Authors should be more precise in reporting the frequency of mutations found in their casistic.

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