Reviewer's report

Title: Identification of novel KCNQ1 and KCNH2 mutations and the protective effect of KCNH2 SNP K897T in Long QT Syndrome families

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Reviewer: Edmund Lee

Reviewer's report:

General: This is an interesting study which investigates the association between potassium ion channel genetic variants and long QT syndrome (LQTS). The authors report two novel mutations, one missense mutation L187P in KCNQ1 and one 2-bp insertion, 2020insAG, in KCNH2 in LQTS families and patients. In addition, they demonstrated a common variant K897T in KCNH2 to be a modifying factor for QTc and that the minor T allele confers a protective effect against prolongation of QTc in LQTS patients. The authors correctly pointed out that controversial results exist in the literature regarding the phenotypic consequence of KCNH2 variant K897. The study examined the effect of K897T on another mutation A490T in KCNH2 using a family-based approach. The present study is a continued investigation in the same cohort of patients enrolled in the authors’ previous study [Chen et al. 2003]. The study is original, the research question is clearly defined, the study design and methods are appropriate, and the data are credible. The manuscript is fairly well written, but some minor amendments are necessary before publication. Consistency is needed in naming genes versus proteins; not all gene names are indicated in italics throughout the manuscript.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

No major critics.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Minor critics:
1. Abstract, methods: the sentence “In this study, we characterized a cohort of LQTS families and patients, for the two large families with LQTS, linkage analysis with markers spanning known LQTS genes was carried out to identify the specific gene for mutational analysis, in a cohort of LQTS patients,” is grammatically incorrect and needs to be restructured. The mutational analysis of the KCNQ1 gene (in the newly-recruited families/patients) should be mentioned here.
2. Abstract, conclusion, last sentence: “VT” should be defined as “ventricular tachycardia” as the term is mentioned here for the first time.

3. Page 3, line 4: “channelopathy” should be spelt as “channelopathy”.

4. Page 3, line 7: “especially under physical, emotional stress or taking QT prolonging drugs.” should be replaced with “when subjected to physical or emotional stress, or upon exposure to QT prolonging drugs.”

5. Page 3, line 10, “…in many cases, the first symptom is sudden death.” should be replaced with “…sudden death may present as the first symptom in many cases.”

6. Page 3, last line from bottom: The typographical errors in amino acid residue designations should be corrected. The sentence should read “…and six known mutations A490T, A561T, D609N, A614V, N629S, and R366X in KCNH2.” Also, references should be cited for these reported mutations.

7. Page 5, mutational analysis: The names (KCNQ1, KCNH2) and region (coding) of the genes should be stated here.

8. Page 6, 3rd line from bottom: “As shown in Fig. 1C, all patients in the family…” the word “patients” should be replaced with “affected members”.

9. Page 7, line 9: “Among mutation carriers, 58% of (18/31) had normal to borderline prolonged QTc…” The word “of” should be deleted.

10. Page 7, line 11: “Mean QTc was significantly prolonged during exercise in gene carriers…” The word “was” should be inserted.

11. Page 8, line 12: “There was no - family history of cardiac arrest and sudden cardiac death.” The “-” should be deleted.

12. Page 9, discussion: The authors should discuss briefly the possible consequences of L187P in KCNQ1.

13. Page 10, line 4: “Functional studies revealed that the mutant channel showed the reduced current density by 39% compared to the wild type channel.” The word “the” should be deleted.

14. Page 10, line 6: The sentence should read “…none of the seven mutation carriers with A490T and K897T showed a QTc > 0.48 s.”

15. Page 10, line 7: “The difference of QTc between A490T alone and combination of both A490T and K897T was notable.” The word “of” should be substituted with “in”.

16. Page 11, 2nd last line from bottom: “The association of SNP K897T with shorter QTc was not without controversy.” The word “shorter” should be inserted.

17. Page 12, line 3: “(0.465 s vs. 0.447 s)” The closing bracket is missing.
18. Page 12, line 10: “The cis-localization between the mutation A490T and SNP K897T in our family vs. trans-localization in the study by Crotti et al. may be one of the potential causes for the discrepancy.” “A490T” should be inserted.

19. Page 12, line 13: The sentence should read “Overall, our results are more consistent with the finding that the minor allele T of SNP K897T plays a protective role against QTc lengthening.”

20. Page 13, line 2: The sentence should read “DNA sequence analysis in the cohort of LQTS families…”

21. Page 13, line 4: “LZ, SR, RB, CO, GV performed the clinical characterization of the patients.” “Perform” should be in past tense.

22. Page 13, line 8: The typographical errors should be corrected. “We are grateful to the family members for their enthusiastic participation in this study.”

Discretionary Revisions (which the author can choose to ignore)

1. The authors may wish to comment on some limitations of the study: (1) The comparison of the mean QTc among carriers with A490T, A490P, and A490T/K897T was made in individuals of different geographical origins under different clinical settings. The accuracy of the analysis might be compromised as the ethnic and environmental influences have not been accounted for. (2) Only the two major LQTS-associated genes were screened in the study population; the effect of the presence of genetic variations in other candidate genes e.g. SCN5A, KCNE1, KCNE2 etc has not been taken into consideration.

2. The authors may wish to discuss the findings from the following papers on K897T in KCNH2.


3. An in vitro functional study to examine the electrophysiological effects of the mutations / combinations of mutations may provide an insight into the molecular mechanism underlying the pathogenesis of LQTS.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have no competing interests