Reviewer's report

Title: Clinical and molecular genetic risk determinants in adult long QT syndrome type 1 and 2 patients

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Reviewer: Kenshi Hayashi

Reviewer's report:

In this manuscript, authors conducted a follow-up study covering a mean of 18.6±6.1 years in 867 genetically confirmed LQT1 and LQT2 patients and 654 non-carrier relatives. LQT1 Finnish founder (FF) mutations KCNQ1 G589D and KCNQ1 c.1129-2A>G, and LQT2 FF mutations KCNH2 R176W and KCNH2 L552S were combined to form the FF mutation population for LQT1 and LQT2, respectively. In mutation carriers, risk factors for cardiac events before initiation of β-blocker included LQT2 genotype, female gender, a cardiac event before the age of 18 years, and QTc ≥500 ms (vs <470 ms). LQT1 patients carrying the KCNQ1 D317N mutation were at higher risk compared to G589D, c.1129-2A>G and other KCNQ1 mutation carriers after adjusting for gender, QTc duration, and cardiac events before age 18. KCNH2 c.453delC, L552S and R176W mutations associated with lower risk than other KCNH2 mutations.

This is an interesting manuscript, however, several concerns need to be addressed to reach the conclusion.

1) Table 1: Authors should show Schwartz score and the QTcs of exercise stress testing.

2) Figure 1 shows that both LQT1 and LQT2 females were more often symptomatic than males. In contrast, Goldenberg et al. analyzed the clinical course of 3779 LQTS patients enrolled in the International LQTS Registry and showed that male gender was independently associated with a significant increase in the risk of cardiac events before age 15 years among probands. They also showed that LQT1 patients exhibit a high rate of cardiac events during the childhood and adolescence periods (Curr Probl Cardiol 2008;33:629-694). There is a discrepancy between these two studies. Authors should explain the reason of this discrepancy.

3) Figure 3, Page 10 lines 8-10: Previous reports showed that mutations in the pore region of LQT2 are associated with higher risk. Authors should divide other KCNH2 group in Figure 3 into KCNH2 mutations in the pore region and those in the non-pore region.
Then, they should compare cumulative probability of cardiac events among these groups, L552S, R176W, and c.453delC.

4) I think authors should not compare cumulative probability of cardiac events between LQT1 and LQT2, because the number of LQT1 patients was 2.5 times many as that of LQT2 patients. In addition, 453 of 617 LQT1 patients had LQT1 Finish founder mutation KCNQ1 G589D.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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