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: Andrew Grace

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Issues regarding management of asymptomatic individuals with LQTS especially with QTs hovering in normal/slightly prolonged range have provided a long-standing issue. The clinical dilemmas have been multiplied as results have emerged from cascade screening. This paper provides useful information to inform clinical decision-making.

Main issues

1. The LQTS locus was first genetically defined in 1996 and even in Finland I assume it took some time to ramp up provision. How does that fit with 18±6 years follow-up of genetically defined phenotype negative populations? To what extent are some aspects of the analysis retrospective?

2. I have always been concerned that stopping and starting beta-blockers may provide risk through a withdrawal mechanism. Is there any evidence to support such an effect here? Also which beta-blockers are being used - selective versus non-selective?

3. What were the indications for ICD? I would push to de-emphasize use based on all we know. So ref. 6 should be referred to critically. Not contemporary with a robust rebuttal through correspondence at the time.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

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?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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