Reviewer's report

Title: Search for Cardiac Calcium Cycling Gene Mutations in Familial Ventricular Arrhythmias Resembling Catecholaminergic Polymorphic Ventricular Tachycardia

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Reviewer: Zahurul A. Bhuiyan

Reviewer's report:

Authors have searched for mutations in the genes (RyR2, FKBP1B, ATP2A2, SLC8A1) presumed to be involved in CPVT pathogenesis in two groups of CPVT patients (confirmed and likely/doubtful). First group comprised 16 patients with typical CPVT features, where authors have found two mutations in RyR2. Second group comprises 17 patients who were reported to have only VPCs, where no mutation has been detected.

Authors have not screened one important gene CASQ2, till now reported pathogenic mutations in CASQ2 are homozygous or compound heterozygous, perhaps this precluded them not to screen the CASQ2.

Overall, it’s a nicely written manuscript.

Several concerns:

A) Authors have included all the coding exons in RyR2. I would suggest to screen the negative patients for the exon-3 deletion, which is not an arduous task. A long segment PCR could easily be done to delineate presence/absence of this deletion in the RyR2 negative cohorts.

B) I would consider it not logical to say septal hypertrophy linked to RyR2 mutation. This has been compared with the extended phenotypes described by Bhuiyan et al (2007). In fact, none of the RyR2 negative carriers reported by Bhuiyan et al. (2007) had any extended phenotypes. In this manuscript by Marjamaa et al., non-RyR2 carriers also have septal hypertrophy, which suggests this phenotype independent of RyR2 mutation.

C) Authors have mentioned that, N3308 in RyR2 is conserved, which is not true. This is not conserved between hRyR1 and hRyR3, not also with the RyR2 from other species. This should be modified.

D) Why only 13% of the patients have a mutation, though previous reports (which includes reports from present authors) detected 40% mutation in RyR2. Was there any selection bias in recruiting patients?

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 declare that I have no competing interests