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: Jonathan G Seidman

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The authors identified 33 consecutive patients with frequent ventricular premature complexes (VPCs) without structural heart disease and frequent history of syncope or sudden death in family. 16 of 33 patients featured exercise induced VPCs, while the other 17 showed VPCs at rest.

The RyR2, FKBP1B, ATP2A3 and SLC8A1 genes were sequenced in all 33 patients. 2 novel CPVT-causing RyR2 mutations were found among 16 subjects in the exercise induced VPC group and a novel RyR2 variant of uncertain clinical significance in a patient with abundant resting VPCs. The mutant N3308S variant RyR2 was tested in vitro.

Major comments;

1) The clinical criteria used to define CPVT is unclear in this manuscript. Do both groups A and B have CPVT? Or Only group A has CPVT? In any event, examples of polymorphic beats on the ECG should be presented. Given that RyR2 variants are found in members of both groups, there is reasonable evidence that the two groups are not particularly different. Perhaps the frequency of sequence variants in RyR2 should be 3 in 33.

2) The nucleotide sequence traces of the three mutations should be presented as supplemental data.

3) The pedigrees of the three families with RyR2 sequence variants should be presented. The pedigrees should indicate the clinical diagnosis and genotype of family members. This can be either supplemental material or placed in the text.

4) Sequence variants S616L and R1051P should also be tested in vitro.

Minor comments;

In table1 and figure 1 legend: Presumably, bmp should be “bpm”.

In table1, the QTc range is up to 470ms. Is this correct? A patient with a QTc of 470ms has a prolonged QT interval; this prolonged QT interval may be responsible for TdP.
Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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.