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: Christopher H George

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This is straightforward study of two small cohorts of patients presenting with CPVT and CPVT-like clinical symptoms. There are numerous mutations in the Ca2+-handling proteins RyR2 and calsequestrin that have been linked to CPVT (and other cardiac pathologies that mimic CPVT), although there is a significant incidence of CPVT in the apparent absence of abnormalities in these proteins. The present study identified two novel CPVT-linked mutations in RyR2 (from a cohort of 16) and one apparent polymorphism in a CPVT-like cohort. Logically, the authors attempted to identify mutations in other Ca2+-associated proteins (FKBP, SERCA, NCX1) to explain a candidate molecular basis for their clinical observations. Unfortunately, this proved a fruitless task.

Accordingly, apart from the discovery of two novel mutations, the study contributes little new to the field. The absence of additional information as to precisely what underscores the clinical phenotype in the absence of RyR2 mutations (and the presumed lack of mutations in CSQ) leaves the study with a disappointing conclusion.

Major compulsory revisions.

The data on what appears to be a functionally normal sequence variant (N3308S) is too preliminary and does nothing to convince that this variant is in any way connected to the disease phenotype. It is misleading, at this early stage, to state that N3308S is an "RyR2 variant that might play a role in the modification of the phenotype".

Why have the authors not investigated the in vitro characteristics of the novel R1051P and S616L mutations that DO appear to be linked with CPVT? This should be done. The authors comments that the mutational loci is not typical of CPVT (i.e. not found in 'hot-spots'). This makes their lack of functional characterisation even more puzzling.

It is very surprising that the authors did not investigate CSQ. From other studies, CSQ is robustly associated with CPVT phenotype and in their previous work they identified polymorphisms in CSQ (EJHG 2003). Given that the present work partly focusses on a benign RyR2 variant, the lack of knowledge regarding the existence of CSQ sequence polymorphisms in these same cohorts is a notable omission.
Minor essential revisions
Figure 1 is poorly explained in the text.

Page 9, paragraph 2 is rather confusing. For R1051P, the index patient's son has a similar phenotype but did he also carry the mutation?

The single channel data should be labelled as Figure 2

p12. Although the work of Bhuiyan is cited, the authors should refer to recent data in which RyR2 mutations have been linked to a longQT-like phenotype.

p4, para 2. The authors should acknowledge the controversy surrounding the RYR2:FKBP12.6 interaction in heart disease

p7 para 2. Is the full-length co-expressed with FKBP12. HEK cells already express abundant FKBP12 so should this read FKBP12.6?

Level of interest: An article of limited interest

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