Reviewer’s report

Title: Exploring digenic inheritance in arrhythmogenic cardiomyopathy

Version: 1 Date: 06 Oct 2017

Reviewer: Petros Syrris

Reviewer's report:

In this revised form of the manuscript by König et al the authors have made significant changes following the reviewers' recommendations. In my view, most comments have been addressed successfully and I have no doubt that the authors have genuinely tried to improve their study. The comments I have specifically made were fully answered. In particular, the addition of a diagram on the bioinformatics analysis is very informative. Also, as far as I can judge there are comprehensive responses to Dr Jongbloed's comments too.

It is worth noting that the introduction of three additional individuals carrying a PKP2 variant has substantially changed the findings of this study. ZRZB are no longer considered as possible disease modifiers, a fact that led to extensive rewriting of the manuscript. This just highlights that studies with a relatively small number of participants can lead to unreliable findings. Dr Jongbloed's suggestion to increase the number of ARVC patients was particularly valid and it is a shame that the authors could not obtain additional samples.

I have two further comments:

The diagram in Fig 2 must now incorporate the filtering performed after adding individuals A, B and C.

I believe the use of the "+-" symbol in the pedigrees (Fig 1) is confusing. As there are no homozygotes, simply having a "+" sign will be enough. The different colours would still indicate different genes/variants.

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
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Yes

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