Author’s response to reviews

Title: Exploring digenic inheritance in arrhythmogenic cardiomyopathy

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Comment from authors:

We would like again to sincerely thank Dr. Petros Syrris and Dr. Jan Jongbloed for the second review of our revised manuscript. We do appreciate the efforts they have made over the last months to help us improve our manuscript. We have addressed the latest minor comments of both reviewers and hope that you find our manuscript suitable for publication.

Apart from the reviewers comments, we noticed that the references in Table 2, column “Comment” were not correctly updated in the first revised version. Therefore, the citations were now corrected in the second revision and match the reference numbering of the main manuscript.
Reviewer reports:

Petros Syrris (Reviewer 1): 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.

Response from authors:

We added the three individuals A, B, and C to Figure 2.

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.

Response from authors:

We replaced the “+-” symbol with a “+” symbol in Figure 1 and also adjusted the Figure legend.

Jan Jongbloed (Reviewer 2): The authors keep using the term "protective" for variants identified in carriers of the PKP2 mutation that are (yet) not affected. I would suggest to not use that, as there is no proof that such variants are indeed protective. Remove this from the discussion section (page 19, line9-14) and the methods (page 8, line 20-26) section (I think the termonology is not used in the results section).
Response from authors:

We removed the term “protective” in both the discussion section and the methods section, as suggested by Dr. Jongbloed. There are no other occurrences of this term remaining in the manuscript.