Reviewer’s report

Title: Exploring digenic inheritance in arrhythmogenic cardiomyopathy

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Reviewer: Petros Syrris

Reviewer's report:

Konig et al have investigated two families with arrhythmogenic cardiomyopathy (ACM) caused by mutations in the PKP2 gene. As it is usually the case with ACM, penetrance of PKP2 mutations in those families is low with some carriers being completely unaffected. To explain this observation other genetic or environmental factors have been proposed including the presence of two (or more) variants which contribute to disease development.

So the authors correctly used whole exome sequencing in an attempt to identify such variants. However, the outcome of whole exome data analysis largely depends on the bioinformatic methods used. A slight modification of filtering during this process would yield a very different set of variants. The filtering strategy employed in this work resulted in 89 and 294 distinct variants in 257 genes in the two PKP2 families. Consequently, the authors had to implement further (arbitrary) filtering concentrating on known ACM related genes and PKP2 related genes. In my view, even though perfectly understandable, this does introduce bias into the results. My suggestion would be to add this in the limitations section to make it clearer.

I would also suggest that the authors include a flow chart or diagram on how the bioinformatic analysis (including filtering) was performed. This could act as a visual aid as, in places, it is not easy to follow the separate steps taken to remove variants/genes.

I believe the conclusion is quite strong and needs to be toned down a bit: "...we have provided further evidence that a single (desmosomal) mutation might not be sufficient to cause ACM..." I think at best this study reports on the co-segregation of some variants with a PKP2 mutation in two families but there is no solid evidence that the identified variants are actually involved in the pathogenesis of ACM.

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?
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Yes
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