Reviewer's report

Title: Missense mutations in Desmocollin-2 N-terminus, associated with Arrhythmogenic right ventricular cardiomyopathy, affect intracellular localization of desmocollin-2 in vitro

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Reviewer: Zahurul A. Bhuiyan

Reviewer’s report:

In this study by Giorgia Beffagna and colleagues have investigated 54 unrelated cases of ARVC for DSC2 mutation/s, where no mutations have been detected in any known ARVC causing genes. Authors have found, in total, 2 missense mutations, which means slightly less than 4% of the studied subjects carried a DSC2 mutation.

Authors also have performed in-vitro trafficking analysis to characterize the pathogenic effect of these two mutations, where they have shown that the mutants are trafficking deficient.

Several queries and suggestions are as follows:

1) Mutation p.E102K: Only the proband fulfills the criteria for ARVC. But, what about the other carriers (father and two brothers), do they have any phenotype pertaining to ARVC? Authors might say that this mutation is less penetrant, but, which to my understanding will not be fully agreeable due to the numbers of unaffected. How is the clinical penetrance of DSC2 mutation carriers described by other authors compared to your findings?

2) I have similar question regarding the second mutation p.I345T.

3) Trafficking analysis: Authors have described that mutation causes halted trafficking. This should be clearly explained. I am sure authors have noticed that after transfection, cells transfected with wild type constructs show membrane localisation, at the same time there are some cells which still have abundant expression in the cytoplasm. This does not mean that this is an intracellular protein, proteins are still not fully trafficked to the membrane.

My question:
Do you see GFP signal ONLY in the cytoplasm in case of both mutants?? This question applies to both p.E102K and p.I345T.

If it is completely intracellular, what will be your explanation about the healthy non-penetrant carriers? Is it not an important component in the ARVC pathogenesis?

What next?: Unable to decide on acceptance or rejection until the authors have
responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**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 interest.