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

Version: 1 Date: 14 August 2007

Reviewer: Ferhaan Ahmad

Reviewer’s report:

General

Beffagna and colleagues have identified two novel mutations in the desmocollin 2 (DSC2) gene in families with arrhythmogenic right ventricular cardiomyopathy (ARVC). Two previous reports of mutations in DSC2 leading to ARVC have already appeared in the literature, including one with functional studies of the mutation in a zebrafish knockdown model. The current study presents some novel mechanistic insights by assessing localization of mutant desmocollin 2 in transfected cardiac myocytes and HL-1 cells. Overall, this study is methodologically sound, even if the significance of the findings is somewhat modest.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

None.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. I believe that the wildtype sequence at nucleotide 1034 is T, so that the codon is ATT encoding isoleucine (I), whereas the mutation at position 1034 is C, so that the codon is mutated to ACT encoding threonine (T). If this is correct, the mutation should be designated 1034T>C rather than 1034C>T throughout the manuscript.

2. To my eye, it appears that the p.I345T protein, like the p.E102K protein, is present to some extent at the membrane. The text implies that the p.I345T protein, unlike the p.E102K protein, is almost absent from the membrane. I am not certain that there is a real difference between the two mutant proteins. In fact, p.I345T does appear to co-localize somewhat with desmoglein, albeit less than wildtype desmocollin-2.

3. It is mentioned in the text that proband II-2, family #149, has left ventricular dilation. This fact is not mentioned in Table 2.
4. Table 2 indicates that the 15-year-old daughter in family #170 has right ventricular abnormalities, but the text indicates that she is fully asymptomatic. To a non-clinical readership, “asymptomatic” may imply completely normal. It may be advisable to reword this sentence.

5. Page 9, line 4. Please add “HL-1” in front of “cells.”

6. Reference 23 is incorrect. This paper appeared in J Cell Biol.

7. Figure 2 legend. Please add “and HL-1 cells” after “two cardiomyocytes.”

Discretionary Revisions (which the author can choose to ignore)

1. How were probands screened for mutations in DSP, PKP, DSG2, and TGFB3?

2. Do the authors feel that the E102K mutation, located in the propeptide region, alters cleavage? This residue is not in the cleavage consensus sequence. The authors may wish to speculate on the mechanism of pathogenesis of this mutation, given that it is not in the mature peptide.

3. Table 2. RV size / function “M” and “m” presumably refer to major and minor diagnostic criteria. Please clarify.

What next?: Accept after minor essential revisions

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

Quality of written English: Needs some language corrections before being published

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.