Reviewer’s report

Title: No evidence for an association between the -36A>C Phospholamban gene polymorphism and a worst prognosis in Dilated Cardiomyopathy

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Reviewer: Maximilian G Posch

Reviewer’s report:

The authors present a genetic association study of a previously identified polymorphism in the phospholamban promotor region in 885 patients with dilated cardiomyopathy and 150 controls. Based on their results the authors conclude that – in contrast to a previous study - the -36A>C polymorphism is not associated with dilated cardiomyopathy.

The strength of the study is the total number of patients included and the detailed clinical data of study subjects. However, there are several major limitations. Major and minor points are listed below.

Major compulsory revisions:

1. The major limitation of the study is the composition of the patient (DC) cohort. The authors state in the title, abstract and in the introduction that they have genotyped 885 patients with Dilated Cardiomyopathy. However according to Table 1 there are only 186 patients with idiopathic DCM. In contrast to the statement in the title, the majority of patients have heart failure due to coronary artery disease, hypertension, chagas disease or cardiac valve defects indicating that the patient cohort is highly heterogeneous, which constitutes a major limitation of the study. The largest subgroup of patients had coronary artery disease (CAD, n=218). However, etiology of CAD is influenced by multiple environmental and genetic factors suggesting that the impact of a single gene polymorphism is very small in these patients; a fact that may contribute to the negative association of the polymorphism. The authors should be aware that dilated cardiomyopathy is a term used for primary disease of the heart muscle which may be caused by genetic mutations (including phospholamban) in some cases. Patients with hypertensive heart disease or CAD should not be termed as “DC” patients. The heterogeneous cardiac phenotypes should also be reflected in the title. Hence, the authors should replace the term “DC” by “Heart Failure” in the title and throughout the manuscript. Furthermore, the number of patients with idiopathic DCM should be considerably increased to account for at least one half of the total number of study subjects.

2. According to table 1 the study cohort also includes patients with different ethnic origins which would be a further chink of the investigation. Where the control subjects matched concerning ethnicity of the probands?

3. The overall numbers of cases and controls are highly dysbalanced (885
patients versus 150 controls). Therefore, the number of controls should be augmented. This is especially important since the overall prevalence of the -36A>C variant is low (only three homozygous carriers among 885 probands).

Minor essential revisions:

1. “worse” instead of “worst” in the title and throughout the manuscript.

2. The title is misleading because the study cohort does not exclusively includes patients with Dilated cardiomyopathy. Therefore, "Dilated cardiomyopathy" should be replaced by "Heart failure".

3. Abstract: First sentence:
To my information CAD and not DC is the leading cause of Heart Failure. This should be corrected.

3. Page 3 (Background):
The first two references are not suitable to support the statement about the epidemiology of DCM. Towbin et al (Ref 1) review the molecular and genetic pathomechanisms of dilated and hypertrophic cardiomyopathies. Geier et al. (Ref 2) present mutations in the MLP gene in patients with hypertrophic cardiomyopathy. These two articles are not at all suitable to document epidemiology of heart failure.

4. I would encourage the authors to cite (and read) the current classification for cardiomyopathies instead of the old one. Thus, they should replace Reference 4 by Maron BJ, et al Circulation; 113:2006 pp.1807-1816

5. The “point genetic variant” is an unusual phrase and should be replaced by genetic variant.

6. The authors refer to the study of Medin et al (Ref 8) who first identified the -36A>C polymorphism in one out of 85 DCM subjects (1.17%) and in 5% of control probands. The allelic frequencies in the study by Medin and colleagues are 0.6% (not 0.5%) in cardiomyopathy patients. Yet, the cohort of the cited study (Ref 8) included patients with hypertrophic of dilated cardiomyopathy. The limited comparability of the present results should be highlighted in the manuscript.

7. Methods: What is meant by the term valvular cardiomyopathy? Heart failure (ventricular dilation) due to valve diseases? I have never heard this term before.


Discretionary Revisions:

1. The authors should explain if the subjects which were homozygous for -36A>C were within the study of control group. Did these patients reveal some unique cardiac features?

2. Table 1: The association of the -36A>C variant should be calculated for the different subgroups of the study cohort (patients with CAD, with DCM etc.).
Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

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