Author's response to reviews

Title: No evidence for an association between the -36A>C Phospholamban gene polymorphism and a worse prognosis in Heart Failure

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Version: 2 Date: 11 May 2009

Author's response to reviews: see over
Dear Prof. Melissa Norton,
Editor-in-Chief,
BMC Cardiovascular Disorders

Please find attached a revised version of the manuscript entitled “No evidence for an association between the -36A>C Phospholamban gene polymorphism and a worse prognosis in Heart Failure” that we would like to re-submit for publication as an original article in the *BMC Cardiovascular Disorders*.

First, we would like to thank the interest of the BMC Cardiovascular Disorders editorial board on our work and the opportunity to re-submit a revised version of the manuscript. In preparing this revised version we have carefully addressed each reviewer’s comment/suggestion. First of all, we genotyped an entirely new sample (1259 individuals) constituted of individuals from the general population. This has certainly improved our understanding about the relationship between this particular genetic marker and population structure and disease association patterns. We would like to highlight that the main goal of this study was to describe the potential association of this functional genetic marker and different levels of phenotypic variation in the scenario of heart failure in general and not to constrain our analysis to a specific etiology “niche”. In this regard, the new experiments proposed by the reviewers and included in this revised version have significantly expanded this aim to a larger spectrum of individuals now ranging from the general population to severely affected heart failure patients. We believe our findings are important in the delineation of the disease spectrum that may be modulated by this particular marker.

We hope this information will be interesting to *BMC Cardiovascular Disorders* readers.

Thank you very much in advance for your kind attention,

Best regards,

Alexandre Pereira
Heart Institute, University of São Paulo Medical School, Brazil
Comments to reviewer Maximilian G Posch:

In his careful revision of our manuscript this reviewer has based his concerns in three main points: 1.) the composition of the patient DC cohort; 2.) if the control population was ethnically matched to the studied patients; 3.) the overall dysbalanced numbers of cases and controls. We will address each major concern separately.

First of all, as pointed by this reviewer the used terminology in the first version of the manuscript regarding Dilated Cardiomyopathy was equivocate in its use. Since the best term describing the used sample would be heart failure (HF) due to the different etiologies present in the sample, instead of DC, we accepted the suggestion of this reviewer replacing the name DC to HF in the title and throughout the manuscript. Regarding the suggestion to increase the account of DC patients for at least one half of the total number of study subjects, we believe this is not necessary since our primary goal was indeed to evaluate the association between the studied genetic marker and different variables capable of characterizing the heart failure phenotypic architecture and not only a specific cardiomyopathy phenotype. We understand that, by being a complex disease, different etiologies of heart failure will be caused and modulated by both different and common, environmental and genetic factors, our main objective was to evaluate if, as previously suggested (Haguigui K, et al.), this functional genetic marker is influencing disease phenotype and progression given that a particular individual already has heart failure. Nevertheless, in this new revised version we have contemplated this concern by specifically testing a putative association between the -36 A/C polymorphism and heart failure (versus a normal control population) and also between each different HF etiology from our cohort.

The reviewer also raises the question about the size of the control population and the different ethnic groups of the case population. To address these two questions, we decided to genotype a large sample of 1259 individuals representative of the Brazilian general population.
In this new version of the manuscript we describe the association between the different subgroups of etiologies, as required, and again we did not found any difference between groups and any difference in each group with the general population sample. It is also important to say that we tested the homozygotes (recessive model) for the -36A>C in HF and in the general population, even with a small number of individuals, and we observed no association with any characteristics in both populations.

All minor concerns were corrected and included in the revised version of the manuscript. In particular, regarding the concerns related to the use of information from the study of Medin et al (Ref 8) we would like to clarify that we were careful in using data from allele frequencies described only in patients with DCM (thus escluding the subgroup of patients with Hypertrophic Cardiomyopathy).

Finally, we would like to thank the careful review conducted by reviewer Maximilian G Posch. It is our feeling that these criticisms have leaded us to significant improvement of the overall quality of our manuscript and have broadened the reach of our description.
Comments to Madhu Khullar:

We have carefully read the reviewer’s report and the two firsts concerns about the diverse etiology of the HF population and the number of control subjects plus the ethnicity match were already discussed in the previous comment.

The unique purpose of table 3 (table 6 in the new version of the manuscript) was to support that medication use at baseline enrollment was not significantly different between genotype groups (thus practically eliminating this as a potential confounder in our analysis).

All the others points discussed by the reviewer were considered and incorporated in the revised version of the manuscript.