Author's response to reviews

Title: Association between UCP2 A55V polymorphism and risk of cardiovascular events in patients with multi-vessel coronary arterial disease

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MS6144397646368746

"Association between \textit{UCP2} A55V polymorphism and risk of cardiovascular events in patients with multi-vessel coronary arterial disease"

Dear Prof. Tim Sands

Executive Editor,

\textit{BMC Medical Genetics}

Please find attached the new revised version of manuscript MS6144397646368746. We appreciated the assistance of the reviewer, and we have made all suggested changes providing a point-by-point description.

We hope this new revised version has reached the high standards of \textit{BMC Medical Genetics} and that it will be interesting to its readers.

\textbf{Reviewer’s comments to author:}

\textbf{Reviewer: Gilberto Velho}

Revision 2 is a much-improved version of manuscript MS 6144397646368746. However, some important ("major compulsory") points of previous comments were not addressed.

1. Methods / Statistical analysis. Stratification of the comparisons by the glycemic status of the patients has a major impact in the results of the study. For this reason, I believe that the authors should not simply ignore it when defining the threshold of statistical significance. As the authors remarked in their response to the reviewers, even with a
conservative correction (i.e. Bonferroni), most of their results would still be considered significant. So, there is no reason for not doing it. Moreover, a more elegant (and less conservative) alternative to Bonferroni’s could be used. It would consist in nesting the genotype variable within the "glycemic status" variable in the Cox regression model. This would result in the computation of statistical effects for normoglycemic and dysglycemic subjects separately, adjusted for multiple comparisons due to the stratification by glycemic status.

We are now providing more data on the significant interaction between glycemic status and UCP2 genotype in determining cardiovascular events incidence in our cohort. For all proposed models a significant interaction term could be observed, suggesting that, at least for our sample, there is indeed a significantly different effect of UCP2 genotype in dysglycemic versus normoglycemic individuals.

2. Results: Text and table 2. As stated by the authors in their response to the reviewers "...we provide the reader with 3 different analyses showing the same results: a frequency comparison using a Chi-square test (used in Table 2). The same comparison using Kaplan-Meier curves (Figure 1) and a multivariate adjusted model provided in the results section". There's one too many. Particularly, because a chi-square test (Table 2) is not appropriate for incidence statistics in prospective studies. It does not take into account the impact of confounding covariable, nor the "time to event" effect. My suggestion regarding table 2 is to keep the genotype frequencies and give the hazard ratios (95% C.I.) and p-values of the Cox regression analyses.

We agree, and now provide on Table 2 only the p-values for the log-rank statistic of Kaplan Meier curves comparison.
- **Minor Essential Revisions**

Tables and text. It is now clear from the data shown in table 2 that the incidence of CAD (all events) between years 2 and 5 of follow-up is relatively stable in dysglycemic VV carriers (year 2: 32.5%; year 5: 36.3%), while it increases in dysglycemic AA/AV carriers (year 2: 20%; year 5: 31.7%). According to table 1, the age of VV and AV/AA carriers is similar at baseline. What about duration of diabetes? This parameter should be given in table 1. The discussion of this issue (page 10) is difficult to understand: "We speculate that the predictive effect of UCP2 genotype in dysglycemic patients could be related to the time since the dysglycemic status has been acquired. On the other hand, there is no experimental evidence suggesting that the duration of diabetes could play a role in this result."

The points listed above were modified according to the reviewer’s suggestions.

Thank you very much for your assistance.

Best regards,

Alexandre Pereira, MD, PhD.

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