MANUSCRIPT NO: 55957

"PNPLA3 and TM6SF2 Polymorphisms in Brazilian Patients with Nonalcoholic Fatty Liver Disease"

Dear Editors,

We appreciate the opportunity to revise our manuscript. We hope we have addressed the reviewer's and editor's concerns to their satisfaction. Please see below our responses to your queries, and the modifications that are highlighted in the manuscript.

Point-by-point response to reviewer's comments:

1. **However, as the authors mentioned the patients size was smaller and only 44% of the patients performed liver biopsy. So the conclusion should be carefully evaluated.**

According to the reviewer's suggestion, we have added to the conclusions that our findings only apply to our sample with histopathological study, and further investigations with larger samples are required to confirm that.

2. **In DISCUSSION section, the authors mentioned: "This finding was different from a previous Brazilian analysis[30], in which NASH occurrence was not associated with the G allele presence in the NAFLD individuals." "This finding suggests that in Brazilian population, the genetic variants of rs58542926 TM6SF2 may have distinct influence on NAFLD than that observed in other populations." Further reasons should be clarified in discussion section.**

The fact that our investigation associated NASH occurrence with the G allele, which was not observed in the previous Brazilian analyses, was further discussed. We believe this finding could be attributed to the fact that the prior Brazilian

study enrolled a small number of simple steatosis individuals (n = 34) and the simple steatosis:NASH proportion was 1.0:6.3, whereas in our study it was 1.7:1.0.

Variant genotypes of TM6SF2 were not associated with NAFLD or NASH occurrence in our investigation. We believe that this finding could be explained by the admixed characteristic of Brazilian population. Previous report have shown that NAFLD subjects in Brazil presented genetic ancestry contribution from European (48.8%), African (41.7%) and Amerindian (9.5%). Besides that, since TM6SF2 minor allele frequency is less frequent in general population (*i.e.*, 7-13%), larger samples may be required to confirm this finding.

Issues Raised by the Editor

1- **The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).**

The grant number was reviewed and the grant application form was added.

2- **The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.**

We arranged the original editable figure using PowerPoint and substituted the figure in the manuscript to the same one presented in PowerPoint so they both have the same design. Feel free to reprocess graphs, legends and text portions.

3- **The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.**

We added the section "Article Highlights" to the manuscript.

Thank you again for the reviewer's suggestions. They really improved the paper.

We are looking forward to hearing from you at your earliest possible convenience.

Sincerely,
Claudia Alves Couto