Point-by-Point Answers to Reviewers

Dear Reviewers:

Please find below the answers to the reviewer´s comments. We greatly appreciate the time and effort spent by the reviewers in conveying their comments and feedback

Torres-Valadez et al. investigated differential distribution of gene polymorphisms associated with hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia among Native American and Mestizo Mexicans. Although the topic may be important to investigate, **Reviewer noted several concerns.**

Reviewer 1.

Q1. It is a well-design study adding new information to the literature. According to my knowledge, it is a novel paper in its field opening new horizons for further evidence. Authors, succeed to present their findings in a clear way. In addition, the object as well as the results are appropriately discussed in the context of previous literature explaining the importance of the manuscript in its field. Authors succeed to present their data in a clear way adding information to the existing literature. Therefore, I have no corrections or further work to propose for the improvement of the manuscript and therefore it can be published unaltered.

Reply: Thank you for your comments

Reviewer 2.

Q1. This manuscript may be better suited for Journals related to lipidology or genetics instead of hepatology.

Reply: The genetic aspects of the dyslipidemias in the context of genomic medicine in hepatology is precisely our line of research. In this study, we investigated how these genetic polymorphisms can modify the outcome of the hyperlipidemic state, considering ethnicity and miscegenation. These lipid alterations occur in the metabolic milieu of the liver and have been related to long-term liver damage. Furthermore, dyslipidemias are

keys drivers of the metabolic syndrome involved in the onset and progression of NAFLD/NASH. Thus, the aim of this study is compatible with the journal's scope. In this sense, two reviewers agreed with its publication in this journal.

Q2. Page 2. Reviewer agreed with the author's statement, "Regional personalized medicine strategies considering the host's genetic and environmental factors are required to mitigate the prevalence of dyslipidemias" if the patients responded poorly to treatment. Regardless of the genetic background, treatment will be same, i.e., diet, exercise, and medication. The genetic background test is expensive and take time.

Reply: Genomic medicine strategies approach both prevention and treatment of diseases considering genetic and environmental risk factors. However, the most important benefit it that it seeks to provide a personalized management to prevent rather than treat advanced disease before a poor response is detected. Knowing the genetic background of the population and its regional differences is crucial for healthcare personnel in the clinical setting. Because the "any diet, exercise, or medication regimen fits all" approach does not apply to every population due to the differences in genes and environment. In this sense, clinical approaches may not be the same worldwide to mitigate these pathologies. Genetic tests may be expensive at the individual level for some countries. However, research and technology are advancing quickly to make feasible this trend in personalized medicine for all populations.

Q3. In Table 3, some genetic data are missing. They are required to discuss heterogeneity of genetic background in different ancestors.

Reply: In this study, several representative populations of West Mexico with different ancestral compositions demonstrated in previous studies were included. While it is true that it was not possible to complete the genetic profile of all populations, the frequencies of risk alleles shown in Table 3 are sufficient to demonstrate a differential distribution of gene polymorphisms associated with dyslipidemias among Native Americans and Mestizo Mexicans. This point is added in the discussion. (Page 15).

Q4. What is "normal weight individuals "?

In Table 4-7, authors showed results from "normal weight" GDL. Please clarify the reason why authors investigate "normal weight" GDL. It will be much

more attractive if authors showed the comparison of these data among NA and MTZ. If authors showed complete data, now authors can describe "Regional primary health care strategies are required to mitigate their prevalence considering the regional genetic and cultural characteristics, which could have important implications for personalized medicine within the new era of precision medicine" in CONCLUSION.

Reply: In Materials and Methods, "Study population and design," section, On page 6: "normal weight" subject was determined by a BMI of 18.5-24.9 kg/m2 and a body fat percentage of <20% for men and <30% for women (Page 6). We have clarified this point in this section to indicate why we investigated the association between hypercholesterolemia and the related SNPs in normal weight MTZ GDL instead of comparing them. A new sentence was added: *This study subgroup was established as a reference population to decipher the influence of these genetic polymorphisms on dyslipidemia since it is a mestizo group with a more balanced genetic ancestry between Native Americans and Europeans*" (Page 6).

Q5. Page 8. In Table 1, average ages among groups looked very different to Reviewer.

Reply: By post hoc tests, only the average age of the TPC group was significantly higher than all other study groups (p=0.002). The average age of the WXK, GDL, CUQ, VP and SMA were similar according to the post hoc test (page 22, footnote table 1)

Q6. Although authors stated, "All the groups had excess weight, but the MTZ groups from GDL and TPC had the highest BMI of all the groups (33.8±10.3 kg/m² and 28.3±4.7 kg/m², respectively, p=8x10-27)", BMI of CUQ was 28.6 and higher than TPC. This is not appropriate expression since highest BMI was from GDL.

Reply: We agree with the reviewer. This variable was appropriately described: "All the groups had excess weight, but the MTZ group from GDL had the highest BMI (33.8±10.3 kg/m2, p=8x10-27) (page 8)

Q7. Page 9. Although authors stated, "On the other hand, the NAH group showed lower levels of HDL-c than those from CUQ and WXK groups (p=0.011)", HDL-C from SMA was lowest.

Reply: We agree with the reviewer. We reviewed the statistical analyzes in Table 2, and this inconsistency was corrected. The correct HDL-c values are now displayed (Table 2, page 22) and the description in the text is also correct.

Q8. More detailed description for statistics analyses for Tables 5 and 6 is required.

Reply: The descriptive statistical analyses for Tables 5 and 6 was more detailed in the Materials and Methods, "statistical analysis" section (page 8). Also, the specific statistical analyses for Tables 5 and 6 are specified in the footnotes (Table 5, page 26; table 6, page 27).

Q9. When compared frequencies of apoB and LDLR genotypes of HChol in Tables 5 and 6, they looked different. Please clarify.

Reply: We agree with the reviewer. The statistical analyses of Tables 5 and 6 were reviewed and rectified. The frequencies of APOB and LDLR genotypes of Hypercholesterolemia are the same in both tables. The percentage differences observed in Tables 5 and 6 are due to the total of the column of each polymorphism. (Table 5, page 26; table 6, page 27).

Q10. Page 10. Authors stated in Results "Also, both genotypes, TT of *APOB* and GG of *LDLR* were associated as independent risk factors for HChol (OR=5.33, 95%CI:1.537-18.502, p=0.008, & OR=3.90 95%CI: 1.042-14.583, p=0.043, respectively) (Table 6)." Please clarify why authors can state "independent risk factors".

Reply: The association of genotype TT of APOB and GG of LDLR was determined by an OR value. Odds ratio (OR) is the measure of association between an exposure (in this case, both genotypes) and an outcome (in this case, HChol). The OR represents the odds that an outcome will occur given a particular exposure compared to the odds of the

outcome occurring in the absence of that exposure (Szumilas M., 2010). However, we agree with the reviewer that the wording of this result may not be precise. These results were appropriately described: "*Also, both genotypes, TT of APOB and GG of LDLR were associated with HChol (OR=5.33, 95%CI:1.537-18.502, p=0.008, & OR=3.90 95%CI: 1.042-14.583, p=0.043, respectively)*" (Page 10)-

Reviewer 3.

Q1. In my opinion, the manuscript was prepared well, so I suggest accepting it in actual form. * The Introduction Section explains the design of the study. The Authors well justify the research topic. * The study was carried out without methodological errors. * The Descriptions of the results were correct. * The presented figures and table were prepared precisely and also legible. * The Discussion Section includes the accurate reference of the results obtained to the studies of other studies. * The Conclusions were well formulated.

Reply: Thank you for your comments.