Answering Reviewers

1. Page 8: "There was extensive impact of PNALA3 SNPs on the serum level of several types of lipid, including cholesteryl ester (CE), free fatty acid (FFA), lysophosphatidylcholine (LPC), lysophosphatidylcholine plasmalogen (LPCO), lysophosphatidylethanolamine (LPE), phosphatidylcholine (PC), choline plasmalogen (PCO), phosphatidylethanolamine (PE), ethanolamine plasmalogen (PEO), and triacylglycerol (TAG) (Table 2)." This statement is descriptive, without specifying the nature of the "impact" on lipid levels. The accompanying Table 2 is complex and it's significance is difficult to interpret. The authors should state only significant changes (compared to controls) in association with a PNPLA3 SNP, either hetero- or homozygous. The term "extensive impact" does not belong in a results section, which should merely state the significant changes. Qualitative statements concerning results should be reserved for the Discussion.

Reply: We are thankful for the reviewer's comments. Revisions have been made according to the suggestion.

In the present experiments, a group of PNALA3 SNPs (rs139051, rs738408, rs738409, rs2072906, rs2294918, rs2294919 and rs4823173) demonstrates significant correlation to various members of cholesteryl ester (CE), free fatty acid (FFA), lysophosphatidylcholine (LPC), lysophosphatidylcholine plasmalogen (LPCO), lysophosphatidylethanolamine (LPE), phosphatidylcholine (PC), choline plasmalogen (PCO), phosphatidylethanolamine (PE), ethanolamine plasmalogen (PEO), and triacylglycerol (TAG) in the sera of nonalcoholic fatty liver disease (NAFLD) patients. Table 2, which is subjected to simplification as suggested, numerically displays the members of SNP-associated serum lipids that have been summarized above. Qualitative statements concerning these results have be presented in the *Discussion*. For example, 'members of TAG, CE and FFA were identified in the differential serum lipids associated with *PNPLA3* SNPs

(e.g., rs738408, rs738409, rs2072906, rs2294919 and rs4823173)', 'PNALA3 rs139051 and rs2294918 exerted their lipidomic impact mainly on the phospholipid metabolites', and 'LPCs, LPCOs and PEs among these ones were confirmed to dominate the differential serum lipids because of their high abundance'.

2. Pages 8-9: The extensive listing of individual lipid changes is redundant, considering that all data is provided in Table 3. The narrative should be shortened to indicate significant changes only, without providing individual values listed in the table. The final statement in this section, "Thus PNPLA3 rs139051 and rs2294918 are suggested to affect the phospholipid metabolite profile, especially LPCs, LPCOs and PEs, in a bidirectional manner", is, again, interpretive and should be reserved for the discussion. Therein, the authors should explain what is meant by the phrase "bidirectional manner".

Reply: We are thankful for the reviewer's comments. Revisions have been made according to the suggestion.

The individual lipid changes are omitted in '*PNPLA3 rs139051 and rs2294918 exerted upregulatory effect on LPCs and LPCOs*' so as to shorten the narrative and avoid the redundant description of experimental results. Compared to those with A/G or G/G genotype, NAFLD patients carrying A/A genotype at PNALA3 rs139051 exhibit significantly higher serum levels of LPC 17:0, LPC 18:0, LPC 20:0, LPC 20:1, LPC 20:2, LPC O-16:1, LPC O-18:1, and significantly lower levels of LPE 20:4, PE 34:0 and PE O-36:5. Analysis also shows significantly increasing levels of LPC 17:0, LPC 20:0, LPC 20:1, LPC O-16:0, LPC O-16:1, and LPC O-18:1 in the NAFLD patients with G/G phenotype, compared with A/A or A/G phenotype, at PNALA3 rs2294918. Quantitative results are presented in the Table 3.

The interpretive statement of 'Thus PNPLA3 rs139051 and rs2294918 are suggested to affect the phospholipid metabolite profile, especially LPCs, LPCOs and PEs, in a bidirectional manner' is removed in the same paragraph.

Alternatively, carful discussion is employed to highlight the different effect of PNPLA3 SNPs (rs139051 and rs2294918) on LPCs, LPCOs and PEs. For example, 'NAFLD patients with A/A instead of A/G+G/G genotype at PNALA3 rs139051 exhibited significantly higher levels of LPCs and LPCOs', 'G/G, but not A/A+A/G, genotype of PNALA3 rs2294918 also predisposed NAFLD patients to statistical elevation of serum LPCs and LPCOs', and 'In contrast to its correlation with LPCs and LPCOs upregulation, G/G genotype at PNALA3 rs2294918 conferred significant lower levels of PEs in the NAFLD patients as compared to those with A/A+A/G genotype'.

3. Page 10, paragraphs 1 and 2: Here again the authors should truncate the narrative to indicate significant changes, without recapitulating data provided in the table. The final sentence is speculative and belongs in the Discussion.

Reply: We are thankful for the reviewer's comments. Revisions have been made according to the suggestion.

Numerical description in '*Low-grade hepatic inflammation occurred in NAFLD patients with A/A genotype at PNPLA3 rs139051*' is truncated for the purpose of indicating significant changes. The final sentence is also removed. In alternative, comprehensive analysis of PNPLA3 genotype and SAF-based pathological grading confirms that an increase in LPCs and LPCOs significantly associates to an attenuation of hepatic inflammation. The protective role of PNPLA3 rs13905 against inflammatory manifestation of NAFLD is also proposed in *Discussion*.

4. Page 12, last paragraph: "Metabolomically" is not a word.

Reply: We are regret for the misspelling of 'Metabolomically'. It should be 'Metabolically'.

5. The entire Discussion should be shortened. For example, the authors could comment on SNP-related changes in lipid profiles in a more general way (eg,

Increased or decreased phospholipid species) without providing the extensive parenthetical insertion of individual changes). These only serve to make the narrative difficult to read in interpret.

Reply: We are thankful for the reviewer's comments. Revisions have been made according to the suggestion.

The *Discussion* has been shortened with a summary of alternation in lipid profile, instead of providing the extensive parenthetical insertion of individual changes. For example, 'NAFLD patients with A/A instead of A/G+G/G genotype at PNALA3 rs139051 exhibited significantly higher levels of LPCs and LPCOs', and 'G/G, but not A/A+A/G, genotype of PNALA3 rs2294918 predisposed NAFLD patients to statistical elevation of serum LPCs and LPCOs'.

6. Page 13, paragraph 1: "…significantly correlated with hepatic inflammation in a reciprocal manner." Please clarify this statement. Again, in the preceding test, avoid the use of extensive listing of individual values in parenthesis.

Reply: We are thankful for the reviewer's comments. Revisions have been made according to the suggestion.

Extensive listing of individual values is removed from preceding test in the revised version of manuscript. The statement of '…significantly correlated with hepatic inflammation in a reciprocal manner' is also subjected to clarification. In brief, our experimental observations relating to NAFLD patients reveal that an increase in LPCs and LPCOs significantly correlates to an attenuation of hepatic inflammation. Moreover, both high-level LPCs/LPCOs and low-grade lobular inflammation characterize patients with A/A genotype at *PNPLA3* rs139051. Pathological characteristics other than hepatic inflammation, including hepatocyte steatosis, ballooning, and liver fibrosis, display no association with either of these phospholipid metabolites.