Reviewer #1: The study of Wang et al is a well performed review reporting studies that support a possible role in PNPLA3 polymorphisms as determinants of response to treatment options of NAFLD. I have a suggestion to improve the quality of the manuscript However, I think that for complex diseases like NAFLD, the effect of any genetic risk variant is unlikely to be sufficient to be clinically meaningful, nonetheless the identified NAFLD risk loci do provide hope for the development of risk algorithms for improved patient stratification and management. Maybe the authors should also address this aspect, the I148 PNPLA3 is one of the genetic variant most associated with NAFLD, but not the only one.

Reply: We are thankful for the reviewer's comments. Careful revisions have been made in line with these comments.

NAFLD is now recognized to be a complex disease with polymorphic association to multiple genes[1]. Limited number of PNPLA3 variant (e.g., rs738409) among these ones has a significant contribution, whereas variants in TM6SF2[2], MBOAT7[3] and GCKR[4] show the moderate-size effects. Besides, large number of variants in APOB[5], APOC3[6], LYPLAL1[7], MTTP [5], LPIN1[8], SOD2[9], UCP2[10], ENPP1[11], IRS1[11], IL28B[12], KLF6[13], MERTK[14], and Irisin[15] action in a low-effect manner. Effect of any risk variant of NAFLD is unlikely to be clinical meaningful. Nonetheless, the identification of NAFLD-related risk loci and the evaluation of variant-dependent difference in treatment response do provide hope for the development of risk algorithms, and also the improvement in patient stratification and management. Given the close association of PNPLA3 polymorphism and NAFLD, the

risk allele of PNPLA3 rs738409 C>G (PNPLA3 I148M) reflects one of the most important genetic variants associated with NAFLD. Its effect on therapeutic efficacy further highlights a potential approach to the precise treatment of NAFLD.

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