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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 57445

**Title:** Validation of genetic variants associated with metabolic dysfunction-associated fatty liver disease in an ethnic-Chinese population

**Reviewer's code:** 03668558
**Position:** Editorial Board
**Academic degree:** MD
**Professional title:** Academic Fellow
**Reviewer's Country/Territory:** Italy
**Author's Country/Territory:** Singapore

**Manuscript submission date:** 2020-07-07
**Reviewer chosen by:** Jia-Ping Yan
**Reviewer accepted review:** 2020-07-18 15:06
**Reviewer performed review:** 2020-07-19 06:34
**Review time:** 15 Hours

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|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good<br>[ Y] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [ Y] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[ ] Minor revision [ ] Major revision [ Y] Rejection |
| **Re-review** | [ Y] Yes [ ] No |
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

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**SPECIFIC COMMENTS TO AUTHORS**

This was a retrospective study which explored the association between single nucleotide polymorphism (SNP) variants in 72 patients with NAFLD. The main finding of this study was that PNPLA-3 GG allele was significantly associated to NAFLD. As acknowledged by the Authors, this study has several limitations. My comments: - What criteria were adopted for diagnosis of NAFLD? Moreover, diagnosis of steatosis has been heterogeneously made – with histology, MRI, CT scan, combination of both…Moreover, only 1% used CAP for diagnosis. This heterogeneity could be an important bias. - 99% controls were identified as having no steatosis using only radiological features. How many were identified as having no steatosis using liver biopsy? - How many patients fulfil criteria for NASH? How many for metabolic syndrome? - This was a retrospective, case-control study. Therefore, terms as "enrolled" should be avoided. Similarly, anthropometric measurements have been retrieved from a database, I suppose. - The Authors said that the BMI cut-offs were 23 and 28 for overweight and obesity, respectively. However, in the result section they used different cut-offs. - Result section: SD for age is missing; total cholesterol, triglycerides…units are missing; PNPLA3: p value is missing - Considering multivariate analysis, the Authors demonstrated that serum TG was an independent predictor of NAFLD. However, as they acknowledged, some patients (36% and 23%, respectively) have been treated with lipid lowering agents. Therefore, it is difficult to provide a clinical value to this result at multivariate analysis. - Introduction: Patatin instead of palatin

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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 57445

**Title:** Validation of genetic variants associated with metabolic dysfunction-associated fatty liver disease in an ethnic-Chinese population

**Reviewer's code:** 03741923
**Position:** Editorial Board
**Academic degree:** MD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Singapore

**Manuscript submission date:** 2020-07-07

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2020-07-11 12:34

**Reviewer performed review:** 2020-07-19 09:08

**Review time:** 7 Days and 20 Hours

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|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [ Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ Y] Accept (General priority)<br>[ ] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [ Y] Yes [ ] No |
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

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**SPECIFIC COMMENTS TO AUTHORS**

In this study, the authors investigated the impact of SNPs with the risk for NAFLD in a Singapore Chinese population and their interactions with environmental and medical risk factors. It is an interesting study. Here, some issues need to be further clarified. 1. Hypertriglyceridemia, high BMI and PNPLA3 GG are independent predictors of NAFLD. Whether do the combination of the three indicators have more powerful predictive ability in NAFLD. 2. For 72 NAFLD cases, what kinds of therapies were performed? 3. How long is the follow-up? During the follow-up, how did the authors monitor these patients? 4. AUROC were 0.823 and 0.789 with and without the PNPLA3, respectively. What are the sensitivity and specificity?

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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 57445

**Title:** Validation of genetic variants associated with metabolic dysfunction-associated fatty liver disease in an ethnic-Chinese population

**Reviewer's code:** 02860653
**Position:** Editorial Board
**Academic degree:** LLB, MD, PhD
**Professional title:** Academic Research, Doctor, Research Scientist, Staff Physician, Surgeon
**Reviewer's Country/Territory:** Ukraine
**Author's Country/Territory:** Singapore
**Manuscript submission date:** 2020-07-07
**Reviewer chosen by:** Jia-Ping Yan
**Reviewer accepted review:** 2020-07-10 08:24
**Reviewer performed review:** 2020-07-22 08:16
**Review time:** 11 Days and 23 Hours

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|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[Y] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [Y] Yes [ ] No |
| **Peer-reviewer** | Peer-Review: [ ] Anonymous [Y] Onymous |

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| **statements** | Conflicts-of-Interest: [ ] Yes [ Y] No |
|---|---|

**SPECIFIC COMMENTS TO AUTHORS**

The manuscript titled `Validation of genetic variants associated with non-alcoholic fatty liver disease in an ethnic-Chinese population` is an interesting study. Topic is novel and of high relevance for the topic of NAFLD and in the scope of the World Journal of Hepatology. However, some points should be carefully reconsidered in the current version. My major concern is that authors simplify the issue and research is biased. The aim considers causality: `to evaluate the impact of single nucleotide polymorphisms (SNPs), previously identified in Western populations, and environmental and medical risk factors on the risk for NAFLD in a Singapore Chinese population.` I would suggest that associations would be more acceptable… Methods. Why did Authors focused on ethnic-Chinese population? Is any evidence on specific development of NAFLD in this ethic group? Group in heterogeneous according to the treatment options. Confounding factors although considered, like comorbidities, smoking, alcohol, etc. largely affect the records. Number of diseases can affect liver function. Comparison to overall population? Why did Authors consider only imaging data (CT, MRI) - `no hepatic steatosis on CT, MRI or CAP score`… Did authors use ultrasound visualization / sonoelastography (other than fibroscan)? Liver biopsy. Adhere point to the existing evidence. If Authors used CT, US, visceral fat measurement could be added? As well as other organs evaluation (relevant and minimally needed), e.g., kidney, parameters of metabolic syndrome. Cohort is too small to make initial conclusions in the matter, in particular for specific pattern in Chinese population. The following issues should be (more) carefully considered and discussed as follows: Authors found that `The subjects who had NAFLD were more likely to have body mass index higher than 24.9 kg/m2.` Why BMI was not inclusion criteria? Stratification on body weight,

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any relevant findings… The issues need to be explained. Patients stratification: • Stratification of metabolic syndrome / obesity/ liver diseases. • Obese vs non-obese vs low BMI cohorts; • Gender, age; • History of receiving drugs (min/max doses), drugs overuse; • Diet; • Next point is the phenotype of individuals, e.g., microbiota ? I recommend to reconsider structure for named avoiding bias, speculative hypotheses and conclusions in the matter; and rather focus on clear associations between particular genetic and phenotype markers. Recommendations for prevention and management future research plan including stratification patients to groups under risk is needed. Extensive limitation paragraphs should be added.

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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 57445

**Title:** Validation of genetic variants associated with metabolic dysfunction-associated fatty liver disease in an ethnic-Chinese population

**Reviewer's code:** 05045866
**Position:** Editorial Board
**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Croatia

**Author's Country/Territory:** Singapore

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**Reviewer chosen by:** Jia-Ping Yan

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**Review time:** 23 Days and 17 Hours

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|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [ Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[ ] Minor revision [ Y] Major revision [ ] Rejection |
| **Re-review** | [ Y] Yes [ ] No |
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

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**SPECIFIC COMMENTS TO AUTHORS**

This research article reports on the validation of the genetic variants, that are known to be associated with metabolic (dysfunction) associated fatty liver disease (MAFLD) in Western population, in an ethnic-Chinese population. It is the first of its kind study in Singapore Chinese population and is valuable as such. However, there are certain facts to be clarified. 1. A new nomenclature has been established for what was known to be Non-alcoholic fatty liver disease (NAFLD) - metabolic (dysfunction) associated fatty liver disease (MAFLD). Please replace the term with the new one in the manuscript. 2. Can the conclusion that more progressive forms of NAFLD can be predicted by PNPLA3 genotyping in Singapore Chinese population be drawn from this study? 3. It is mentioned that the effect size for SNPs other than PNPLA3 is likely to be too small to be clinically significant. What is the effect size of PNPLA3 gene polymorphism on MAFLD? 4. How was the sample size calculated?