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315-321 Lockhart Road, Wan Chai, Hong Kong, China

## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 8873

**Title:** Pooled genetic analysis in ultrasound measured NAFLD in Indian subjects: a pilot study

**Reviewer code:** 02079515

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 16:55

**Date reviewed:** 2014-01-13 01:26

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

A well written and interesting study



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## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 8873

**Title:** Pooled genetic analysis in ultrasound measured NAFLD in Indian subjects: a pilot study

**Reviewer code:** 02541859

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 16:55

**Date reviewed:** 2014-01-20 10:38

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

file attached.



**ESPS Peer-review Report**

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

**ESPS Manuscript NO:** 8873

**Title:** Pooled genetic analysis in ultrasound measured NAFLD in Indian subjects: a pilot study

**Reviewer code:** 02541437

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 16:55

**Date reviewed:** 2014-01-23 00:22

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> [ Y]Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> [ Y]Minor revision
<input type="checkbox"/> [ Y] Grade E (Poor)	<input type="checkbox"/> [ Y] Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> [ Y]Major revision
		<input type="checkbox"/> No records	

**COMMENTS TO AUTHORS**

Genetics play an important role along with metabolic factors in the development of NAFLD. Ultrasound has low specificity and sensitivity for NAFLD. Further association studies should be done with liver biopsy.

**ESPS Peer-review Report**

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

**ESPS Manuscript NO:** 8873

**Title:** Pooled genetic analysis in ultrasound measured NAFLD in Indian subjects: a pilot study

**Reviewer code:** 00742517

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 16:55

**Date reviewed:** 2014-01-24 22:53

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ Y] Grade B (Very good)	[ Y] Grade B: minor language polishing	[ ] Existed	[ Y] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ] Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

**COMMENTS TO AUTHORS**

The manuscript of ‘Pooled genetic analysis in ultrasound measured NAFLD in Indian subjects: a pilot study’ investigates the genetic susceptibility of nonalcoholic fatty liver disease (NAFLD) on a basis of GWAS. Nineteen SNPs in genes of PNPLA3, APOC3, COL13A1, PARVB, SAMM50 and PZP, etc. are resultantly filtered to be associated with the ultrasound-proved NAFLD in Indian subjects. Besides, significant association of rs2073080, rs343062 and rs6591182 with high BMI, rs2854117 and rs738409 with high triglyceride levels and rs2073080, rs2143571, rs2228603, rs6487679, rs738409 with high ALT levels have also been presented. These findings may add a new level to our knowledge about the genetic basis of NAFLD, especially in the Indian population, and be valuable for clinical interference. Major comments 1. According to the Abstract, NAFLD and control groups are recruited on the basis of standard criteria for NAFLD and ultrasound findings of fatty infiltration. The criteria for NAFLD, however, have not been described in the MATERIALS AND METHODS. If Indices of glycolipid metabolism (as shown in Table 2), such as glucose, insulin, total cholesterol, HDL, LDL, etc., reflect the criteria for NAFLD, formula concerning these indice should be clearly mentioned. Otherwise, authors have to make it clear that NAFLD is evaluated solely by the ultrasound findings, in accordance to the description that ‘subjects were recruited based on ultrasound findings of hepatic steatosis as per earlier reports’ (Page 5). 2. SNPs with p value <0.05 are considered to be statistically significant in this study. In contrast, rs738409 of PNPLA3 (p=0.05), and rs2143571 of SAMM50 (p=0.05), is reported to associated with NAFLD and high triglyceride level, respectively. Is there any discrepancy? Minor comments 1.Nonalcoholic fatty liver disease instead of its abbreviation, namely NAFLD, maybe suitable for the title of manuscript. 2.SNPs, rather than the genes in which they located, should be listed in Table 3. 3.Rows with header are suggested in Table 5.

**ESPS Peer-review Report**

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

**ESPS Manuscript NO:** 8873

**Title:** Pooled genetic analysis in ultrasound measured NAFLD in Indian subjects: a pilot study

**Reviewer code:** 02860544

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2014-01-11 16:55

**Date reviewed:** 2014-01-27 13:13

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

**COMMENTS TO AUTHORS**

This study aimed to investigate genetic susceptibility in Indian subjects with non-alcoholic fatty liver disease (NAFLD) by performing a pooled genetic study. Using significant SNPs from GWA studies reported from different ethnic populations for NAFLD, the authors in their case-control study revealed the association of SNPs in PNPLA3, PARVB, SAMM50 and PZP genes with NAFLD and SNPs in PARVB, APOC3, PNPLA3, SAMM50, NCAN, PZP with high BMI, triglyceride and ALT levels. They suggest that these genetic risks could help clinicians to identify susceptible individuals at an early stage to provide better management of the disease. Although these findings seem to be novel, there are still some issues to be clarified.

Major 1. The authors did not state that how were these cohort recruited? What were the reasons these subjects visited the Hepatology clinics of the hospital? Do they have other metabolic comorbidity such as diabetes, dyslipidemia, or hypertension? Were these subjects recruited consecutively or selected on some basis? These issues are very important because selection bias can occur to distort the study results.

2. As the authors stated in the Material and Method Section, the major limitation of this study is that they use ultrasound as the diagnostic tool for NAFLD, instead of the good standard biopsy or other advanced imaging techniques. Therefore, the authors should describe what were the diagnostic criteria for NAFLD, and how to avoid the inter-observer variability?

Minor 1. Table 2 described the demographic and clinical characteristics of the study subjects. However, no data of lipid profiles, blood pressure, fasting plasma glucose, and percentage of subjects with hypertension and diabetes were given. The authors should show these informations.

2. In the Material and Method Section, the authors define low levels of high density lipoprotein as HDL less than 50 mg/dL in males and 40 mg/dL in females.



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This is completely different from the commonly used definition, that is 40 mg/dL and 50 mg/dL in males and females, respectively. 3. The legend of Table 4 is misleading. If the SNPs were independent variables, and BMI, TG and ALT were dependent variables, this table indicated “Significant SNPs associated with higher Odds of obesity, TG, and ALT (but not NAFLD)”. 4. We suggest the authors to merge the information provided in Figure 2 into Table 5.