Reviewer's report

Title: Genetic variant I148M in PNPLA3 is associated with severity of nonalcoholic fatty liver disease in Chinese population

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Reviewer: Luca Valenti

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Yiling Li et al.

Genetic variant I148M in PNPLA3 is associated with severity of nonalcoholic fatty liver disease in Chinese population.

In this paper, Yiling Li and coworkers evaluated the association between the I148M variant of PNPLA3 and the severity of steatosis in 203 Chinese subjects with nonalcoholic fatty liver disease (NAFLD) with ultrasonographic estimation of liver fat content. They confirmed in this population that the frequency of the 148M variant was higher than in 202 matched controls, and found that the frequency of the 148M variant increased with the severity of steatosis, and that there was a significant interaction between PNPLA3 genotype and BMI in determining ALT levels in patients with NAFLD.

They conclude that the I148M PNPLA3 variant is associated with the severity of NAFLD in Chinese population.

The study, though severely limited by the ultrasonographic evaluation of liver fat content, and by the fact that the association between the PNPLA3 I148M variant and NAFLD risk in China has already been reported by some of the Authors (ref. 16) and other groups (ref. 15), and the association with the severity of steatosis was confirmed in multiple population by a recent meta-analysis (ref. 18), represents a nice confirmation of the association of the 148M with the susceptibility to steatosis in a Chinese population, and adds interesting novel information on the association with severe steatosis and on the interaction of PNPLA3 genotype with body mass.

Major compulsory revisions:

1. The methodology adopted to quantify liver steatosis by ultrasonography, and inter- and intra-operator variability of the determination, should be reported in details, as this is a key outcome the study.

2. As "severity of NAFLD" usually denotes the histological severity of liver damage including necroinflammation, hepatocellular damage, and fibrosis, the conclusions should be modified to, e.g. "the PNPLA3 I148M variant is associated with US determined severity of steatosis in a Chinese population"

3. As severity of steatosis was the main outcome of the study, it would be important to know whether there was a significant interaction between PNPLA3
and BMI towards the severity of US determined steatosis.

4. Discussion: most of the patients with NAFLD included in the study had increased liver enzymes and/or moderate/severe steatosis, accepted indications for liver biopsy; therefore it cannot be stated that biopsy could not be performed for ethical reasons.

Minor discretionary revisions:

1. It is worth noting that the 148M variant was associated with reduced LDL levels in patients with NAFLD. Can the Authors comment on that based on recent findings by other groups (e.g. Kollerits 2009, Palmer 2012)

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

No competing interest to declare