Reviewer’s report

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

Version: 1 Date: 24 July 2012

Reviewer: Carlos Pirola

Reviewer’s report:

Major compulsory revisions:

A major concern is that the authors considered disease severity in NAFLD as the degree of steatosis by ultrasonography. This is a major mistake, disease severity in NAFLD only can be assessed by liver biopsy. The “severity of NAFLD” is not studied in this work. At best, grade of steatosis, but even this is not appropriately measured because it is a variable hardly quantified by ultrasound, which is very subjective. In fact, the PNPLA3 variant and disease severity was associated with disease severity (simple steatosis vs NASH) in biopsy-proven patients for the first time in 2009 (cite 24) soon after the first report done by Romeo et al in their GWAS (cite 10).

The genotyping method should be better described and Hardy-Weinberg equilibrium data provided. In the statistical section, some paragraphs required clarification, in particular, how adjusted p values are calculated.

The major outcome is the figure showing that the effect of the gene variant seems to be dependent on BMI, but number of patient should be clearly indicated in each genotype group for every BMI percentile. Owing to the small number of patients enrolled, a false positive is likely, therefore an a priori power estimation should be done.

In the discussion, again, authors used “severity of the NAFLD” and affirmed wrongly that its association with the variant is inconsistent in the literature. The effect of I148M PNPLA3 variant is one of the strongest and most replicated ever reported for a common variant in any complex disease.

Minor essential revisions:

In the background section some phrases are confusing, i.e. “multiple genes have been associated with NAFLD”. This reviewer assumes that authors refered to GWAS because the list of citations is very limited and there is a number of candidate genes studies also performed. Please add additional evidence or rephrase.

Level of interest: An article of limited interest

Quality of written English: Acceptable
**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests