Reviewer’s report

Title: Chromosome 1p13 genetic variants antagonize the risk of myocardial infarction associated with high ApoB serum levels.

Version: 2 Date: 15 June 2012

Reviewer: Orestis Panagiotou

Reviewer’s report:

Major Compulsory Revisions

1. As a reader, I feel that the authors should explain in more detail why the 3 specific SNPs were selected for genotyping and examination for modifying MI risk. E.g. rs660240 as well as other SNPs in the same gene region and/or loci are also associated with lipid levels. Same question applies to SNPs in other regions. In the current manuscript it is not clear enough what the selection criteria were: e.g. whether the strongest SNPs in each locus were selected, etc. The possibility of selective reporting cannot currently ruled out: i.e., the authors have tested many SNPs but the report here only those with positive results. Also, it would be useful to report the OR for MI that pertains to the 2 SNPs as these were found in the cited papers (in the Introduction section), especially in the largest studies or in meta-analysis of GWA studies. Hence, one could compare the risk in the current population against the GWAS and see whether the effects are replicated in the SHEEP.

2. I am not sure why an SI=0.62 (0.34-1.12) provides evidence of antagonism. The 95% CIs are on both sides. Is the interpretation somewhat different?

3. It would be useful if the authors could report the allele frequencies of the SNPs examined, as these were found in their population.

4. Does the result about HWE refer to cases, controls or both? Also, they should report which threshold was used for HWE (P=0.05 or 0.1) and which the P-value for each SNP was.

5. A few more descriptive information regarding the baseline characteristics from Table 1 could be reported in the main text.

6. I think that the authors should present the results of interaction analyses for LDL and Total-Chol. After all, they are more clinically relevant than ApoB.

7. Having said the above (point 6), I would suggest moving the results for the overall population from Supp Table 2 to the main text; especially ORs for ApoB should be presented. Sex-specific results could remain in the suppl.

8. It is not clearly enough described why the authors use median (IQR) and non-parametric tests to compare lipid levels in cases and vs controls? Are these traits non-normally distributed in their population? Or is there some other reason?
Similarly, I would expect to see the effect of the selected SNPs on lipid levels through a linear regression. Is there a reason why they have not performed such an analysis? This could give a more clear picture about the change in lipid levels according to the number of the reference allele.

9. Is the additive model used in the analysis the same as a per-allele model?

10. The limitations of the current work should be more clearly acknowledged.

Minor Essential Revisions

1. Gene names should be written in italics.
2. There should be some footnote explaining what the parentheses in table 1 refer to: is it SDs, percentages etc?

Discretionary Revisions

1. Maybe the authors would find it useful to comment on the cumulative evidence that is likely to be produced in the future from GxE analyses and underline the importance of evaluating this evidence, as potential implications for future research.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests