Approval: Yu-Ching Cheng

Reviewer's report:

**Title**: Genetic variants associated with circulating MMP1 levels near matrix metalloproteinase genes on chromosome 11q21-22 in Taiwanese: interaction with obesity

**Version**: 2  **Date**: 14 November 2012

**Reviewer**: Yu-Ching Cheng

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Major Compulsory Revision:

1. Authors identified two SNPs (rs1799750 and rs495366) to be significantly associated with circulating MMP1 levels. The two SNPs have LD D' = 0.736, which suggests that the two SNPs are still moderately correlated with each other. Have the authors examined whether the two SNPs represent two "independent" signals for circulating MMP1 level in Taiwanese? Does the strength of association for any of the two SNPs change/diminish while including the other SNP in the model simultaneously? Also, in the conclusion of the abstract, authors wrote "genotypes/haplotypes around MMP1 locus are independently associated with MMP1 levels in Taiwanese". Need to consider revise the conclusion pending on the results of suggested analyses.

2. In the haplotype analyses, 10 possible haplotypes were inferred based on 5 SNPs. Given that only rs1799750 and rs495366 showed significant associations with MMP1 in the population (and they are in moderate LD with each other), it seems to be appropriate to also conduct a haplotype analyses based on the two SNPs only and see if 2-SNP haplotype have a better association signals than the 5-SNP analyses. In addition, one advantage of using 2-SNP haplotype is that the number of possible haplotypes tested can be greatly reduced.

3. I found the interaction analyses showing the effects of rs1799750 and rs495366 (as well as the haplotype) present only in non-obese intriguing. Authors further suggested that that "it is possible that obese subjects, who have high levels of many metabolic and inflammatory risk factors, may mask the genetically associated changes (the middle section of page 15). Have the authors actually looked at whether MMP-1 levels differ between non-obese and obese individuals in the study population? I suggest authors add this result in the results section to support this point of view.

4. In the last sentence of the discussion section: “Because our evidence suggested an association between MMP1 gene polymorphisms, MMP1 levels and various diseases, ......” (page 17). Have the authors actually looked at the association between MMP1 polymorphisms and diseases/clinical outcomes (e.g. cardiovascular diseases, metabolic syndromes... etc) in the study population? I didn’t see authors provide any data on this. If the data is available, please add analyses looking at the associations between SNP, MMP1 and these clinical outcomes. If no data is available, please remove “various diseases” from the
conclusion sentence since this remark can be misleading.

5. For SNP association, it is more appropriate to use Bonferroni-corrected $p=0.01$ instead of $p=0.05$ to define significance level given that 5 SNPs were tested in the study.

Minor Essential Revisions:

1. Page 3: line 3 in the abstract “To elucidate genetic determinants….” This is an incomplete sentence. Please re-phrase.

2. Do authors have any data on the Coefficient of Variation (CV) for all the inflammatory assays used in the analyses (e.g. CRP, SAA, sCIAM1, sVCAM1, SELE, MCP1, SELP, sTNFRII, IL6, MMP1, MMP2 and MMP9)? If available, please include the assay CV information in “Laboratory Examination and Assays” section in the Method on page 8/9.

3. Supplement Table 1: please reduce the decimal places used in the numbers (2 decimal places should be sufficient)

4. Table 1: Please add footnote to indicate what comparisons were the p-values referred to? Compare the difference in clinical characteristics between men and women (or not)?

5. Table 5:

(a) Please indicate which allele is the effect allele used in the analyses (i.e. the beta coefficient obtained is estimated based on which allele);

(b) The footnote is incorrect: “coefficient and p values were estimated based on haplotype trend regression…..” The table is results of single SNP analyses, not haplotype analyses.

6. Please provide a short description on how haplotype were inferred in the statistical analyses section (e.g. what algorithm/software package).

Discretionary Revision:

1. Consider moving Table 2 to supplemental material.

2. Please consider using consistent allele coding for rs1799750 deletion/insertion variant (1G/2G). Authors use 1G and G interchangeable to represent the “deletion” allele throughout the text. This can be confusing because 1G/2G can also be annotated as -/G, for which G is actually the “insertion” allele. Please use 1G instead G consistently throughout the entire paper.

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

**Quality of written English:** Needs some language corrections before being published

**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.