Author's response to reviews

Title: Lack of association of two common polymorphisms on 9p21 with risk of coronary heart disease and myocardial infarction

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Version: 2 Date: 31 May 2008

Author's response to reviews: see over
Editor

It is our understanding from the reviewers reports that there are three key issues that need addressing for further consideration within BMC Medicine:

1) Examine whether the lack of the family history of coronary heart disease and myocardial infarction may be a factor for the negative result.
   - We examined the issue. The association is not significant neither in those with a family history of CHD nor in those without a family history of CHD. The results of this analysis is now added to results section (figure1).

2) Analysis should be conducted considering the age of the patients.
   - We performed a sensitivity analysis by limiting the cases to those that developed CHD or MI under the age of 70. The association was not significant in either case. Moreover, we repeated the analysis in subgroups of age. The SNP was not associated with CHD or MI in any of the subgroups.

3) Concerns with the controls. While we appreciate that it will be difficult to obtain angiographic evidence or a full follow up of these patients, we advise that at a minimum the lack of clarity in the control group should be explained in a limitations section.
   - We appreciate the concern and tried to evaluate the issue by comparing the association in those who have a history of cardiovascular disease and those who don’t. However, the SNPs were associated with a more preventive effect in those who did not have a history of CHD (figure 1).
Reviewer: Edith Feskens

Major Compulsory revisions:
1. To increase the strength of the paper sufficiently, the allele frequencies of the prevalent cases should be shown
   - We have now added the minor allele frequency of the SNPs in MI and CHD cases in table 2.

2. Cox analyses with age rather than time on the axes should be conducted or alternatively, only cases occurring before age 70 should be analyzed.
   - We added a sensitivity analysis to the manuscript where the cases are limited to those who developed CHD or MI under the age of 70. The association was not significant. Moreover, we performed the analysis in subgroups of age, however, the association was not significant in any of the age subgroups.

3. Number of cases in text and Table 1 should be similar. The fact that these are different now does not enhance the credibility of the results.
   - We have now checked the numbers in the text to be consistent with the tables.

4. The paper is also easier to read if results of additive model are included in table 2 as well.
   - We have added the results with additive model to table 2.
Reviewer: Qing Kenneth Wang

The authors should provide a comprehensive discussion of all publications related to the study topic. In particular, several recent positive replication studies were not discussed or cited.

Minor Essential Revisions
1. The authors made an error about the position of the SNPs. They are on 9p21, not on 9q21 as stated in the title and other places. This again emphasizes the importance that the authors should read relevant papers and ensure the accuracy of information from other papers.
   - We have corrected the position of the SNP through the manuscript.

2. Please add a column to show P values in Table 1.
   - Two columns are added to Table 1 to show the p value for CHD and MI cases.

Major Compulsory Revisions
1. A comprehensive discussion or introduction should be provided and recent publications by other groups should be discussed and cited.
   - We have added the recent publications to the manuscript both in the introduction and the discussion.

2. Discussion, 4th and 5th paragraph: The authors should examine whether the lack of the family history of CHD and MI may be another factor for the negative result. In the recent J Hum Genetic publication, Shen et al. found that if the whole cohort was divided into those with family history and those without, the association was detected only in the sub-cohort with family history.
   - We examined the issue and added the results to the manuscript (figure 1). The association is not significant in any of the subgroup.