Author’s response to reviews

Title: A study of the association of rs12040273 with susceptibility and severity of coronary artery disease in a Chinese Han population

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Reviewer reports and Our Responses

Emanuela Bostjancic (Reviewer 1): In an article by Yang et al, authors described association of one single nucleotide polymorphism to the susceptibility and severity of CAD in Chinese Han population. Study was performed as a case-control study on 199 CAD patients and 112 non-CAD controls. However, there are certain suggestions that would improve the manuscript.

- One of the limitations of the study that should be mentioned in the Discussion section is that case and controls are not age and gender matched.

Response: Thank you for your good question.

We are very sorry for the limitation in age and gender matching in our study. Due to the volume of coronary angiography in our hospital, the recruiting of controls is difficult. Even so, we adjusted for differences in the age and gender in the statistical analysis procedure to reduce the effects of age and gender in our study. The detailed information has been added in the part of Statistical analyses and Discussion in the revised manuscript with colored markers.
- Another limitation of the study would be a postulated cut-off »less than 30% of narrowing of large branching as non-CAD controls«. Could you perform a reference? Since Gensini score defines stenosis severity of < 25% and 26-50% and these two categories (30% and 25%) are overlapping each other.

Response: We thank the reviewer for these helpful comments.

In most published literatures, the diagnostic criteria of CAD was more than 50% of narrowing of large main or branch coronary arteries. To choose the typical and extreme phenotype of controls, in our study, we strictly those with less than 30% coronary stenosis as healthy controls for the less chance to develop CAD in the near future.

- For elevated amount of HDL-C in healthy adults there are some publications that gender and age influence blood amount of HDL-C. Therefore, although on a small cohort of samples, it would be of great importance to perform distribution of genotype among sex and age in control population. And re-calculate all the statistics.

Response: Thank you for your good suggestions.

Multivariate analysis of general linear model was performed to adjust the effects of sex and age.

- More detailed description of genotyping.

Response: Thank you for your helpful suggestion.

The detailed methods of genotyping was added in the manuscript in the part of DNA extraction and genotyping which read “A 5% samples was selected randomly for sequencing to confirm the results of genotyping.”.

- Based on these results, it is overestimated to conclude that this SNP is preventing for CAD susceptibility.

Response: Thank you for your good question.

We have corrected these statements in the part of Conclusion in the revised manuscript.

- There are numerous grammatical errors.
Response: Thanks!

We have invited a professional editor to help us to improve the language quality.

Cyril Mamotte (Reviewer 2): The question posed is reasonable enough. Is there an association between the rs12040273 polymorphism with susceptibility and severity of coronary artery disease in a Chinese Han population, and taking a lead from findings in a GWAS study.

The main limitation, in my view, is that the study is not sufficiently powered to exclude an effect. The very broad confidence intervals for the OR for CAD highlight this. That the study is limited in such a manner is conceded by the authors in the paragraph preceding the conclusion, and had the authors conducted a power calculation it may have been evident prior to beginning the study. But no power calculations were carried out. A greater number of subjects, particularly of controls is required.

These comments put into context my response to the tick box questions above (i.e. the study doesn't have the necessary controls, and nor do the data therefore support the conclusion).

Response: Thanks a lot for these helpful comments.

We are sorry for lacking power calculation before the study was carried out. The power of our finding to reject null hypothesis was 20% in our study. To draw a convincing conclusion is unreasonable. The related information was added in the Discussion part, the last paragraph before CONCLUSION.

In addition to that there were a number of other flaws. There was a significant difference in sex and gender between the CAD and control groups. That alone invalidates comparisons of a number of variables which are well known to vary with age (e.g. dyslipidaemia, hypertension).

Response: Thank you for your good question.

Due to the relatively small volume of coronary angiography in our hospital, recruiting of controls is difficult. Even so, age and gender was adjusted in the part of Statistical analysis to reduce the effects of age and gender in our study.

Dhanasekaran Bodhini, PhD (Reviewer 3):

Information about the following should be included

a) Whether sequencing was done to confirm the genotyping
Response: Thank you for your reviewing.

We added these helpful information in the revised version. In our study, 5% of the samples were selected randomly for sequencing to confirm the accuracy of genotyping in our study, and the accuracy rate was 100%.

b) Power of the study to detect the significant difference in the HDL levels

Response: Thank you for your good question. We calculated the power of our finding by Openepi software (http://www.openepi.com/), and the power to receive null hypothesis is 83.62%.