Author's response to reviews

Title: Association of the single nucleotide polymorphism in chromosome 9p21 and chromosome 9q33 with coronary artery disease in Chinese population

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Response to reviewers

Reviewer #1

1. Please comment on potential impact of CV risk factors on kind of plaque (quote on PMID: 26508517)

Reply: We agree with the reviewer and now discuss the issue in the Discussion section.

On page 5,

Accumulating evidence came to conclusion that the incidence of hypertension and diabetes, higher inflammatory response and LDL levels are the risk factors for atherosclerotic progression.12 Furthermore, based on optical coherence tomography, cholesterol, hs-CRP and pentraxin 3 were associated with thin-cap fibroatherma, which is known as vulnerable plaques.12-14 Similarly, some of these known risk factors were referred to as independent determinants of CAD in our study.

2. No explanation of the role and function of the genes present on the two loci (9p21 and 9q33) is given. It would be useful to give some information about these in the Introduction and try to add some possible explanations on the pathogenetic role of mutations.
Reply: We thank the reviewer for the suggestion. The known function and potential atherogenic effects of these genes are now demonstrated in the Introduction section.

On page 3,

Most of SNPs on 9p21 are located within a long non-coding RNA, namely antisense non-coding RNA in the INK4 locus (ANRIL). It seems plausible that the influence of ANRIL on CAD is mediated by the upstream genes CDKN2A and CDKN2B. The dysfunction of CDKN2A and CDKN2B subsequently causes excessive cell proliferation.

DAB2IP is considered as a Ras-GTPase activator and a tumor suppressor gene, repressing tumor proliferation and metastasis and maintaining chromosomal stability.

3. Among cardiovascular risk factors included in the first table with Baseline characteristics, no data about familiarity for coronary artery disease (CAD) is presented. Since the authors underlined the importance of the genetic substrate in the history of CAD in the Introduction, some information about family history should be given in the article.

Reply: We acknowledge that the family history of CAD is important in this study and now supplement these data in Table 1. However, we did not find a significant between-group difference in the frequency of the family history.

Minor issues

4. In section "Results", no comments about data should be done, such as "surprisingly (...)"

Reply: As suggested, we now rephrase these inappropriate words.

5. It would be useful to include a table showing all variables that entered the logistic univariate analysis.

Reply: Thank you for your suggestion. It should be noted that we only performed multivariate analysis adjusting for the significant risk factors. Therefore, gender, age, history of smoking, rs1333049, diabetes mellitus, fasting glucose, hypertension and hyperlipemia enter into multivariate analysis.

6. In table 2 and 3 there is not a legend explaining neither the statistical analysis nor the significance of abbreviations

Reply: We acknowledge these errors and now supplement the legends in corresponding tables.
Reviewer #2

1. References are written quite long. All references should be corrected according to journal's instructions for authors.

Reply: As suggested, the pattern of references has been modified according to journal’s instructions.

2. At the end of the article, there are no explicit spellings about abbreviations. For example, what does DAB2IP, WTTCCC, CDKN2A, CDKN2B, ANRIL mean?

Reply: As suggested, we now list the abbreviations at the end of the text.

List of abbreviations

AMI: acute myocardial infarction
ANRIL: antisense non-coding RNA in the INK4 locus
CAD: coronary artery disease
CDKN2A/2B: cyclin dependent kinase inhibitor 2A/2B
DAB2IP: DAB2 interacting protein
GWAS: genome-wide association studies
ORs: odds ratios
SNPs: single-nucleotide polymorphisms
WTCCC: Welcome Trust Case Control Cohort study

3. The ‘discussion’ section of the article was very short, and the findings of the study should be discussed in detail in the context of the literature.

Reply: We agree with the reviewer and discuss previous findings and our results in detail.

4. Written English should be written and reorganized. For example, what does 'replicating studies' mean?

Reply: We have corrected the grammar and typesetting errors throughout the text.
5. Which type of diabetes disease is the 'diabetes' disease among coronary artery disease risk factors? 'Diabetes mellitus'? Or 'diabetes insipidus'? 

Reply: We must explain that diabetes mellitus is the established risk factor for coronary artery disease.