Author's response to reviews

Title: Association between HIF-1alpha C1772T/G1790A polymorphisms and cancer susceptibility: An updated systematic review and meta-analysis based on 40 case-control studies

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Author's response to reviews: see over
Dear Editors and Reviewers,

Thank you very much for your letter and detailed valuable suggestion on our manuscript entitled “Association between HIF-1α C1772T/G1790A polymorphisms and cancer susceptibility: An updated systematic review and meta-analysis based on 40 case-control studies” (Manuscript number: 2003748191956639). The suggestions are quite helpful for us. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers’ comments are listed below this letter.

The major changes are highlighted in the revised manuscript. We hope that the revised version of the manuscript is now acceptable for publication in your journal.

Thanks and Best regards!

Yours sincerely,

Peng Zhao
Responses to the quests:

Replies to Reviewer #1:

Major Compulsory Revisions:

(1). The number of studies included is still not clear. The author state their analysis is based on 41 studies, but there are only 40 studies for the first polymorphism and 30 for the second SNP and the 30 studies appears to be a subset of the 40 studies.

Response: Thanks for the reviewer’s careful insights. We apologize for this negligence. We have corrected the error and scrutinized the rest of the manuscript.

(2) The authors state that they cannot calculate the LD for the two SNPs, because they don’t have the raw data. The authors should be able to look up the pairwise in LD in a publically available source, such as HAPMAP.

Response: Thanks for the reviewer’s professional recommendation. We have searched the “SNAP-Broad Institute” (http://www.broadinstitute.org/mpg/snap/) and found that C1772T is not in substantial linkage disequilibrium (LD) with G1790A ($R^2=0.002$), and we have provided that in our revised manuscript.

(3) The authors should provide the number of cases and controls with each genotype in
Table 2 and Table 3.

Response: Many thanks for the reviewer’s comments! We have included the number of cases and controls for each genotype in the revised tables according to the reviewer’s advice. Moreover, we also have re-edited Table 2 and 3 to make it succinct and clear.

(4) The authors need to address why their results differ from published GWAS in the discussion.

Response: Thanks for the reviewer’s professional recommendation. As the reviewer said, we can conduct a meta-analysis with the GWAS data instead of relying on published data, and the results will be much more reliable. We agree with the views of the reviewer very much. We performed a computerized literature search of the NHGRI GWAS catalog (http://www.genome.gov/26525384), UCSC Genome Browser website (http://genome.ucsc.edu/cgi-bin/hgGateway) and dbGAP, however, we haven’t found any GWAS studies for these two polymorphisms. So we provided it as a limitation in the discussion in our revised manuscript. Further molecular studies are warranted to clarify the relationship between C1772T/G1790A polymorphisms and cancer risk.

Minor Essential Revisions:

(1). There are a couple typos in that statistical methods section: “mode” should be “model” on line 6 of the paragraph and “AA” should be “GG” for the heterozygote
comparison on line 10 (I think).

*Response:* Thanks for the reviewer’s careful insights. We apologize for these mistakes. We have corrected the error and scrutinized the rest of the manuscript.

(2). In the introduction, the author state that there are 35 SNPs in the region, the authors should clarify this by saying “35 common SNPs” and indicate the population.

*Response:* Many thanks for the reviewer’s comments. We are so sorry for this mistake. We have corrected it in our revised manuscript accordingly.

Discretionary Revisions

1. The manuscript would benefit from having a native English speaker review the text.

*Response:* Many thanks for the reviewer’s comments. We have gone over the English with the help of a native English speaker and then improved the style of writer English in our revised manuscript.

**Replies to Reviewer #2:**

(1) I suggested that they should group the three studies that used the same controls (ref.
29) as one in the analysis for the whole population. Actually, it is not so according to Figure 2 and Figure 3 in the revised manuscript.

Response: Thanks for the reviewer’s professional recommendation, we have used the same controls as one in the analysis for the whole population in our revised manuscript and revised Figure 2 and Figure 3 as you suggested.

(2) Additionally, the authors did not list the number of sample size for each comparison which I think it is very useful for indicating the power of the results.

Response: Many thanks for the reviewer’s comments! We have included the number of cases and controls for each genotype in the revised tables according to the reviewer’s advice. Moreover, we also have re-edited Table2 and 3 to make it succinct and clear.

(3) In addition, it is questionable that the author “Ailin Lu” was deleted and the author “Ning Liu” was added in the revised manuscript, which was contradictory with the section of Authors’ Contributions.

Response: Thanks for the reviewer’s comments! We apologize for this negligence. We have corrected the error in our revised manuscript.