Author's response to reviews

Title: The TERT rs2736100 Polymorphism and Cancer Risk: A Meta-analysis Based on 25 Case-Control Studies

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Author's response to reviews: see over
Dear Prof. Zhao,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the link below. Do let us know if you have any problems opening the file.

Referee 1:
http://www.biomedcentral.com/imedia/1145560520629445_comment.pdf
Referee 2:
http://www.biomedcentral.com/imedia/1381992296631491_comment.pdf

Comments to be passed to the authors:
The article to be revised by the authors as suggested by the reviewers in a point-wise manner and should be highlighted in a revised manuscript

Editorial request:

1) Copyediting - : Please note that BioMed Central journals are not copyedited prior to publication. We advise you to pay close attention to language during revision of this manuscript. If necessary, please seek the assistance of a fluent English speaking colleague, or have a professional editing service correct your language. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/info/authors/authorfaqs#12.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 9 December 2011. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.
Dear Editors and Reviewers,

We highly appreciate the detailed valuable comments of the referees on our manuscript of ‘MS 1029078956592742 (The TERT rs2736100 Polymorphism and Cancer Risk: A Meta-analysis Based on 24 Case-Control Studies)’. The suggestions are quite helpful for us. We have modified the manuscript accordingly, and the detailed corrections are listed below point by point.

The major changes we have made including: (1) we rewrote the discussion section; (2) We updated one study into our meta-analysis according to the reviewer’s comment and all the results were also updated including tables1-4 and figure 1-6 ; (3) the manuscript have been edited by a professional language editing agency.

The major changes are highlighted in the revised manuscript. We hope the Reviewers and the Editors will be satisfied with our responses to the ‘comments’ and the revisions for the original manuscript.

Thanks and Best Regards!

Yours sincerely,

Peng Zhao
**Responses to the quests:**

**Reviewer 1: Dr. Kshitij Srivastava**

**Discretionary Revisions**

1. In the results section, \( P=0.00 \) should be replaced with exact value or written as <0.001 (page 7).
   
   Many thanks for the comments. We have revised it in the results section.

2. The authors can include “Supplementary” before Table 1 on page 7.
   
   Many thanks for the comments and we agree with your suggestion. However, when we prepare our manuscript according to author’s instruction “the manuscript formatting, tables, figures and additional files should be referred to in the text and table less than two sides of A4 in length can be included within the body of the published article”, considering the structural integrity and smooth reading, we prefer to put table 1 in manuscript rather than in supplementary.

**Minor Essential Revisions**

1. Provide full name of CLPTM1L gene

   Many thanks for the good suggestion. We have provide full name of CLPTM1L gene- *cleft lip and palate transmembrane 1 like* (page 4) accordingly in our manuscript.

2. The authors have included detailed description of lung cancer subtypes and references in results section. The paragraph should be placed in introduction or discussion part of manuscript (page 8 and 9).

   Many thanks for the wonderful advice. We have revised it as suggested.

3. The authors can include recent articles (after June 2011) on TERT rs2736100 polymorphism in their analysis.

   Thanks for the reviewer’s wonderful good recommendation which is undoubtedly helpful to our manuscript.

   According to the reviewer’s suggestion, we searched recent articles in PubMed, Embase, CNKI, and the Chinese Biomedicine Database. One article (after June 2011) on TERT rs2736100 polymorphism met the inclusion criteria and have been added into our Meta-analysis. In total, 25 case-control studies in English with 23032 cases and 38274 controls was included in our Meta-analysis. So, all the results including tables1-4, figure 1-6 have been revised. A significant association between the TERT rs2736100 polymorphism and cancer susceptibility was revealed by the results of the meta-analysis of the 25 case-control studies. Moreover, increased cancer risk in all genetic models was found after stratification of the SNP data by cancer type, ethnicity and source of controls.
4. TERT gene has a lot of polymorphisms. Why authors have specifically adhered to rs2736100 polymorphism is not clear throughout the manuscript. To date, many studies reported the associations of TERT polymorphisms and cancer susceptibility such as rs2736100, rs2853676, rs2735940, rs2853669, rs2736098 and rs2242652. The reason why we focus on rs2736100 is described as follow: 1) there are more studies related to rs2736100 polymorphism than other TERT polymorphisms suggesting its potential involvement in cancer aetiology among different population subgroups; 2) The role of rs2736100 as a genetic marker for cancer risk assessment is conflicting and the functional significance of the TERT rs2736100 was still unclear, so this meta-analysis will help us better understand its contribution to cancer development. We have addressed this part to our manuscript. 3) We deeply agree with your comments and will pay more attention to the other TERT polymorphisms in our future work to get more information about their roles in cancer aetiology as you suggested.

Major Compulsory Revisions
1. Functional studies on TERT rs2736100 polymorphism should be included and discussed in the manuscript.

Thanks for the good suggestion. We agree that it is better to discuss the potential function of TERT rs2736100 polymorphism in the manuscript. However, it seems difficult to find even one functional study on TERT rs2736100 polymorphism although we have tried our best. So it will be challenging to identify the precise mechanism by which the TERT rs2736100 polymorphism contributes to cancer development. Maybe future studies will give more information.

2: The manuscript is written in a very abrupt manner. The manuscript should be edited by a native English speaker or otherwise by a professional editing agency.

Many thanks for the comments. The manuscript has been edited by a professional language editing agency as suggested.

Reviewer 2: Dr. Hemant Bid
1. In the present study how the variants with significant associations by meta-analysis were assessed and by which criteria?

We assessed the association between the TERT rs2736100 polymorphism and cancer risk according to Venice criteria\(^\text{ref}\), which suggested that 3 factors should be considered to assess the published literature: amount of evidence, consistency of replication, and protection from bias.

2. In the abstract section methodology and conclusion should be discussed in more detailed.  
   Thanks for the good suggestion. We have revised it in our manuscript according to the reviewer’s advice.

3. Under the background this sentence seems incomplete “Lung cancer is the leading cause of cancer death”  
   Thanks for the reviewer’s careful insights! We have corrected this mistake accordingly in our manuscript.  
   In the revised section, we started with the sentence: “Cancer is a multifactorial disease, which is the result of complex interactions between inherited and environmental factors. In our meta-analysis, most of the cancer types were lung cancer and glioma. Lung cancer is the most common malignancy and the leading cause of cancer deaths for women and men worldwide.”

4. Did all the methods were based on guidelines proposed by the Human Genome Epidemiology Network for systematic review of genetic-association studies.
   Yes, all methods were based on guidelines proposed by the Human Genome Epidemiology Network for systematic review of genetic-association studies. The methodology for undertaking our meta-analyses can be found in the HuGE Review Handbook.


5. Under the heading "Data extracted" some information is mission and if authors include these points that will give a better insight and clarity of the study
   It is really a good suggestion. We have added the genotype counts for cases and controls accordingly (as shown in table1), and it will give a better insight into our study.

6. For the evaluation of meta-analysis results did the authors included a test of heterogeneity, sensitivity analyses, and examination for rule-out bias?
   Thanks for your comments. Sensitivity analysis, test of heterogeneity and cumulative meta-analysis were performed in our meta-analysis in results section. Begger's funnel plot and Egger's test were performed to assess the publication bias of literatures. As shown in Figure 6, the shapes of the funnel plots did not reveal any evidence of obvious asymmetry. The results of Egger's test still did not show any evidence of publication bias (t=1.03, P=0.313 for GG versus GT+TT).
7. Limitations of this research study must be addressed?

We have addressed limitations of this meta-analysis in discussion section (as mentioned in the fifth paragraph of the Discussion).

8. What is the justification not to include rs2853676 TERT polymorphism in the current meta-analysis?

Many thanks for the comments. TERT rs2853676 is also an important SNP, which maps to intron 2 of TERT and is in weak LD with rs2736100, and these two SNPs are independently associated with cancer susceptibility. In our meta-analysis, we focus on TERT rs2736100 mainly because 1) There are more studies include rs2736100 polymorphism compared with TERT rs2853676, that is, we can get more data and information to perform our meta analysis. 2) The role of rs2736100 as a genetic marker for cancer risk assessment is conflicting and the functional significance of the TERT rs2736100 was still unclear, so this meta-analysis will help us better understand its contribution to cancer development. We have addressed this part to our manuscript.

9. The first paragraph of Discussion is very generalized

Many thanks for the comments. We have rewritten the discussion section.

10. Discussion part is not properly discussed and need to rewrite?

Thanks for the good recommendation. According to the reviewer’s suggestion, we have rewritten the discussion part which will help readers to better understand this article.