Author’s response to reviews

Title: Association between 20q12 rs13041247 polymorphism and risk of nonsyndromic cleft lip with or without cleft palate: a meta-analysis

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Author’s response to reviews:

Dear PhD Didem Ozdemir-Ozenen, BDS, MDS, DipFHID, MPaed Dent RCS, FDSRCS, PhD, Jayakumar Jayaraman, PhD Aline Petrin

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editors and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “Association between 20q12 rs13041247 polymorphism and risk of nonsyndromic cleft lip with or without cleft palate: a meta-analysis” (OHEA-D-19-00681).

We have studied reviewers’ comments carefully and the comments are all valuable and very helpful for revising and improving our paper. We have made revision which marked in red or using track changes in the paper. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Yunpu He
E-mail: heyunpu1377@163.com
List of actions:
1. As suggested by reviewer 1, we have added a table about the results of the quality of assessment of each article using Newcastle-Ottawa Scale in our revised manuscript (page 19, table 2).
2. We have revised the number (n=14) in Fig 1 about the full-text articles excluded (page 22, Fig. 1).
3. Many grammatical and linguistic errors have been revised (marked in red or using track changes in the paper). Our manuscript was edited by Biji MJ Language Editing Services.
4. We have added an author in paper (line 4, page 1).
5. In the revised version, we have deleted the data about Mixed population (line 19-20, page 2, line 17-18, page 8).
6. As suggested by reviewer 1, we have classified the ethnic groups basis of the country (8 China population as East Asian population, 2 Caucasian as an ethnic, pooled other country population as 13 overall population). We have analyzed the subgroup data were East Asian, Caucasian and overall population, also changed the forest plot and funnel plot figure (page 15-20, page 6, table 1 and table 3, Fig. 2-6).
7. In the revised version, we have made the aim and conclusion match. We deleted the allele and genotype data in the conclusion, just clarify the relationship between rs13041247 and NSCL/P. The statistical data of the result section was made simply (line 13-21, page 2).
8. We have modified the objectives to find the relationship between this SNP and NSCL/P (line 1-2, page 5).
9. This analysis therefore reaffirmed and expanded upon this prior study, expanding the number of included studies to 13, thus yielding a larger sample size that produced some results inconsistent with those of the previous study (line 13-15, page 10).

The point-by-point response to the comments is given below (Reviewer’s comments in red).

Reply to Reviewer 1
Thank you for your constructive criticisms that have helped us to improve our manuscript.

Comment 1: The article requires major language revision. I find difficult to comprehend several sentences throughout the manuscript.
Response: Thank you for your suggestion. Many grammatical and linguistic errors have been revised (marked in red or using track changes in the paper). Our manuscript was edited by Biji MJ Language Editing Services and made major language revision.

Comment 2: Abstract: The aim and conclusion do not match. The authors have mentioned the allele and genotype as well as ethnic variations in the conclusion that is not part of the aim. The Result section is too elaborate with the statistical data which makes difficulty in following.
Response: We have re-written this part according to the Reviewer’s suggestion. We have made the aim and conclusion match. We deleted the allele and genotype data in the conclusion, just clarify the relationship between rs13041247 and NSCL/P. The statistical data of the result section was made simply (line 13-21, page 2).

Comment 3: Introduction: This section must include a brief note on the clinical importance of establishing the association of polymorphism in NSCL/P patients. The aim does not match with the conclusion. I suggest the authors to modify the aims and objectives accordingly.
Response: We have modified the objectives to find the relationship between this SNP and NSCL/P. The results of this study have the potential to guide genetic counseling in families at risk of or affected by NSCL/P (line 1-2, page 5).
Comment 4: Methods: What is the basis of classifying the ethnic groups? The authors in Table 1 have included "Indians" (Ref. 5) in Caucasian group and "Mexicans" (Ref. 8) and "Brazilians" (Ref. 7) in mixed ethnic group. The reason for this segregation must be clearly explained with appropriate references. In addition, the authors have categorized one Brazilian study wrongly in Caucasian group (Ref.12). This error must be corrected and changes made must be appropriately reflected in the results and throughout the manuscript.

Response: Thank you for your suggestion. (1). The article (Ref. 12 Clarissa Fontoura et.al 2012, Ref. Sequence change Ref. 10) said that genotyped 812 Brazil population were Caucasian individuals. (2). Imani MM et.al conducted a meta-analysis (Ref. 20) include “Indians” in Caucasian group and “Mexicans and “Brazilians in mixed ethnic group. (3)We have re-written this part according to the Reviewer’s suggestion. We have classified the ethnic groups basis of the country (8 China population as East Asian population), 2 Caucasian as an ethnic, pooled other country population as 13 overall population (line 15-20, page 6, table 1 and table 3).

Comment 5: Results: The results of the quality of assessment of each article using Newcastle-Ottawa Scale must be presented in the form of a table.

Response: Thank you for your suggestion. We have added table 2. Quality assessment scores for the studies included in this meta-analysis (Newcastle-Ottawa Scale) in our revised manuscript (page 19, table 2).

Comment 6: Discussion: The authors have indicated a similar study with 10 articles has been published earlier. The authors must clearly indicate how addition of three articles in your study has improved the knowledge on understanding the polymorphism in cleft patients.

Response: We have re-written this part according to the Reviewer’s suggestion. This analysis therefore reaffirmed and expanded upon this prior study, expanding the number of included studies to 13, thus yielding a larger sample size that produced some results inconsistent with those of the previous study (line 13-15, page 10).

Comment 7: Figure 1. The numbers in the Eligibility criteria do not match. The Full-text articles excluded, with reasons should be (n=14).

Response: We have made correction according to the Reviewer’s comments (the number should be n=14). We have revised the number (n=14) in Fig 1 about the full-text articles excluded (page 22).

Reply to Reviewer 2

Comment 1: The article adds to the known literature about MAFB role in clefting etiology. The authors seem aware of the limitations of the study. The high heterogeneity among the case-control studies included in the analysis is a potential problem.

Response: Thank you for your suggestion. Because the overall population analysis had high heterogeneity among the case-control studies, we conducted the ethnicity-based and five different genetic models subgroup analyses. We found the high heterogeneity was come from China population (East Asian), leading to the use of a random effect model. Sensitivity analyses were conducted by iteratively omitting individual studies from the overall analysis, while funnel plots were used to examine the risk of publication bias. No significant changes in the study outcomes were detected in a sensitivity analysis, and no evidence of publication bias was detected based upon Egger’s test (East Asian P=0.253, Caucasian P=0.239, and Overall population P=0.124). Similarly, no funnel plot asymmetry was detected.

Comment 2: I suggest a throughout language review before publication.

Response: Many grammatical and linguistic errors have been revised (marked in red or using track
changes in the paper). Our manuscript was edited by Biji MJ Language Editing Services and made major language revision.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red or using track changes in revised paper. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.

Considering the Reviewer’s suggestion,
Special thanks to you for your good comments.
Looking forward to hearing from you.
Thank you and best regards.
Yours sincerely
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