Author's response to reviews

**Title:** Association of TPH-1 and TPH-2 genes with suicidal behavior: A systematic review and meta-analysis

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**Author's response to reviews:** see over
Reviewer's comments

Reviewer 1: Gang Zhu

This is an interesting meta-analysis about the association of gene polymorphisms and SB. If the revisions recommended to the authors as below are finished well, it should be considered for publication in this Journal.

1. The range of title seems to be a little larger. In my opinion, “Association of TPH-1 and TPH-2 gene polymorphisms with suicidal behavior: A systematic review and meta-analysis” is better. We agree, thanks for the comment (Page 1, lines 1-2).

2. Pay attention to the details since some minor mistakes were found in your manuscript, e.g. line 6 at page 7: (3) should be (4); “relevant” at line 17 in page 13 is beyond understanding; “and to integrate” at line 20 in page 13 should be changed to “by integrating”. We agree, we corrected these mistakes (Page 14, lines 8).

3. Please add 1-2 subheads before the first and second paragraphs in accord with the latter subheads--TPH-1 gene variants and TPH-2 gene variants. We added some subheads in this section.

4. The purpose and function of Fig. 2 was not explained clearly in the first paragraph of Results part. We agree, we have explained them now in more detail (Page 9, line 4).
5. You said “we also explored all populations in a combined way” at line 20-21 in page. I just find p values for cases and controls, but find no related results for all population. We corrected this mistake and added the p values on Tables 1 and 2.

6. Most contents at line 3-11 in page 10 should be moved to Methods or Discussion part, since they are not study results. Please state detailed study results about TPH-1 at this paragraph. We agree, we changed this part to the end of the Data extraction section. (Page 8, lines 1-8).

7. In general, fixed effect model is used when heterogeneity is small, while random effect model is used when heterogeneity is big. However, you used random effect model many times when heterogeneity is not obvious. Why?
Response: We added some extra information to clarify this issue (Page 15, lines 2-5).

8. Discussion section is too shallow. Something should be discussed detailedy and prominently, e.g. the innovation stated at line 9-12 in page 16 was too general, how many new data were included in your manuscript should be explained. What is other innovation of your study? This is very important. We deeply appreciate the reviewer’s suggestion; therefore, we addressed the issue of the innovation of our study in the Discussion section (Page 13, lines 17-22).
9. The conclusion sentences at line 21-23 in page 16 did not seem to be sound. The reason why the results should be interpreted with caution is not exact. We rewrote this sentence in order to clarify the point (Page 17, lines 14-18).

Reviewer 2: Zainab Samaan

General comments and essential revisions

1. Grammatical and sentence structure revision. Consider revising the following: a. Abstract: “The study provided evidence that A218C/A779C TPH-1 variants may be a risk factor to manifest for SB at the clinical level” (Page 2; Paragraph 3, Line 17). We agree. This was corrected. (Page 2, lines 17-19).

b. Introduction: “Suicidal behavior has become a public health issue worldwide” (Page 4, Paragraph 1, Line 1). Suicidal behavior isn’t a new public health issue. We suggest to place this introductory statement in context and describe if the trends are increasing or stable. We agree, we corrected this sentence taking into consideration this suggestion. (Page 2, paragraph 1, line 2-4).

c. Discussion: “In addition, we performed a sub-analysis...” (Page 14, Paragraph 1, Line 4), “We also conducted a sub-analysis...” (Page 14, Paragraph 2, Line 22). It should be sub-group analysis. The mistake was corrected in these sentences. (Page 14, line 20; page 15, line 15).
2. In addition, some statements need clarification: “TPH-1 gene variants showed a significant difference” (Abstract, Page 2, Paragraph 2, Line 14). Did you mean significant association? In which direction? This point was corrected.

3. References also need to be added in some areas. For example: a. Introduction: “Even though there are previous meta-analyses…” (Page 5, Paragraph 2, Line 21). These meta-analyses should be cited. This point was corrected.

b. Discussion: “Various published studies show the search for possible genetic markers…” (Page 13, Paragraph 2, Line 11). Please cite these published studies. Response: We added the references to support this statement.

4. A clear definition of SB and a description of how SB was defined among included studies should be addressed, preferably in the Introduction. What specific symptoms are required for a diagnosis? Over what time period? Were any specific assessments used for diagnosis (i.e. SCID, M.I.N.I., etc.)? We added extra information following this suggestion. (Page 3, lines 7-15).

5. The Methods section does not mention the use of fixed effects models however they are found in your results and tables. This should be indicated in the methods, as well as an explanation of why both random and fixed effects models were employed. We added some extra information to clarify this issue (Page 14, line 24; page 15, lines 1-5).
6. Justification for excluding the studies by Yoon & Kim, Zhou, and Zupanc based on heterogeneity needs to be decided a priori and described in the Methods so that the analysis is not results driven. We deeply appreciate the reviewer’s suggestion; we clarified the exclusion a priori in Page 8, line 17.

7. Has the concept of the “virtual” control group been used in previous studies? If so, please cite them. This point was corrected. We added this reference (page 7, line 21).

8. Please clarify the association found between A218C and A779C variants (TPH-1) in the Results section (i.e. positive or negative). Include the corresponding OR, CI, and p-values for all results reported. We modified this point based on the suggestion made by reviewer Gang Zhu.

Discretionary revisions
1. Consider adding a table to outline the exact search strategy that was used in each electronic database.