Author's response to reviews

Title: Association between brain-derived neurotrophic factor genetic polymorphism Val66Met and susceptibility to bipolar disorder: a meta-analysis

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Author's response to reviews: see over
Dear editors and reviewers,

Thank you very much for your good suggestions and instructions. We carefully read the comments from reviewers and revised our manuscript accordingly. We would like to resubmit it for your kind consideration. Enclosed please find our revised manuscript entitled “Association between brain-derived neurotrophic factor genetic polymorphism Val66Met and susceptibility to bipolar disorder: a meta-analysis” [MS: 1848493359141258].

We would like to express our sincere thanks to the three reviewers for their constructive and positive comments. Point by point responses to the reviewers’ comments are listed below.

Sincerely yours,

Zuowei Wang
Reviewer #1: Iria Grande
No comments or suggestions.

Reviewer #2: Janusz Rybakowski
1. In view of the ethnic differences, the mean genotype distribution (Val/Val, Val/Met and Met/Met) in Caucasian and Oriental population should be presented
Response: Thanks for pointing this out. The mean genotype distribution in Caucasian and Oriental population was presented in Table 2.

2. As an example of ethnic differences, the association of this polymorphism with lithium prophylactic response may be given, with positive findings in Caucasian population (Rybakowski et al, 2005; Dmitrzak-Weglarz et al, 2008) and negative in Oriental ones (Masui et al, 2006).
Response: Thanks for your kind suggestion. This question had been considered by us before. Because of the following two reasons, we thought that those three studies were not suitable for a meta-analysis.
(1) The positive findings in Caucasian population (Rybakowski et al, 2005; Dmitrzak-Weglarz et al, 2008) were from one study team, and the samples of two studies were overlapped.
(2) The duration of lithium treatment and the definition of lithium response were different between the study in Caucasian population and that in Japanese population.

3. In abstract (line 16-19) “association of Val66Met polymorphism” should be replaced with “association of Val allele”.
Response: Thank you for pointing this out. We have corrected it as suggested.

Reviewer #3: Gustavo Vazquez
1. It is not clear to me how many patients were included in the analysis. In the Results section, it is stated that 7,219 BPD cases and 9,832 control cases were analyzed. However, the Discussion states that there were a total of 14,438 patients and 19,664 control cases in the meta-analysis. Which version is correct?
Response: Thank you for pointing this out. In total, 7,219 BPD cases and 9,832 control cases were included in the meta-analysis. We have corrected it in the first paragraph of Discussion as follows:

With a total of 7,219 patients and 9,832 control cases, our meta-analysis included an additional 4,076 BPD cases and 3,485 healthy controls compared to a previous meta-analysis of case-control studies [22].

2. Including some type of sensitivity analysis would be a useful way of evaluating the robustness of the results that were found. Perhaps a one-study removed strategy or a cumulative strategy, to evaluate whether the results are being driven by any one specific study?

Response: Thanks for your kind suggestion. We have added the sensitivity analysis of one-study removed strategy into statistical analyses, and reported the results correspondingly.

A sensitivity analysis of one-study removed strategy was used to evaluate whether or not the results are being driven by any one specific study, and a funnel plot was used to detect whether or not there is evidence of publication bias.

The sensitivity analysis showed that the results were not being driven by any one specific study, and the funnel plot did not detect any evidence of publication bias (Figure 2).

3. There is no assessment of the extent to which publication bias may play a role in the observed results. A funnel plot (plotting the observed effect sizes as a function of precision/variability) will help detect whether there is evidence of publication bias. Given that there are a large number of studies with relatively large variation in sample size, it would be useful to assess whether or not publication bias is present. If publication bias is found to be present, could use a technique like Duval and Tweedie’s trim and fill to assess how effect size shifts when hypothetical negative studies are included.

Response: Thanks for your kind suggestion. We have added the funnel plot to assess whether or not the publication bias is present, and reported the results correspondingly.
A sensitivity analysis of one-study removed strategy was used to evaluate whether or not the results are being driven by any one specific study, and a funnel plot was used to detect whether or not there is evidence of publication bias. The sensitivity analysis showed that the results were not being driven by any one specific study, and the funnel plot did not detect any evidence of publication bias (Figure 2).

4. Allelic distributions of the Val66Met polymorphism were compared between different bipolar subtypes and healthy controls, but were compared within the different bipolar subtypes. Perhaps comparing BP I vs. BP II, BPI vs. RCBD, and BP II vs. RCBD would reveal interesting results.

Response: Thanks for your kind suggestion. We have compared the difference between BP I and BP II in the revised manuscript. However, considering only one study about RCBD has been published until now which is not suitable for meta-analysis, we omitted the results about association between RCBD and the Val66Met polymorphism, and so did not compared the difference between BP I or BP II vs. RCBD in the revised manuscript. A post-hoc analysis did not find a significant difference in allelic distribution of Val66Met polymorphism between BP I patients and BP II patients with a pooled OR of 1.10 (95% CI: 0.98-1.25, Z = 1.58, P = 0.12) (Figure 4).

5. Given the repeatedly demonstrated effect of gender on the rates and phenomenology of bipolar disorder, it seems that a gender-stratified analysis might prove to be an interesting analysis in addition to the ethnicity-stratified analyses.

Response: Thanks for raising the comment. As reported, BP II and RCBD may be more common in female population than in male population, but the effect of gender on the rate of BPD is not as important as that of major depression. In addition, all studies included in this meta-analysis did not report respective allele frequency and genotype distribution of the Val66Met polymorphism in male and female population. So we thought a gender-stratified analysis would not be necessary.

6. In the discussion, the authors mention that the non-significant results may be due to limited power of the study owing to the inclusion of only case-control studies. I am
unconvinced by that hypothesis given the large number of patients analyzed in this study.

Response: Thanks for kind comments. This following sentence has been deleted:
“suggesting that meta-analyses only including case-controlled studies, like the present study, may not have enough power to detect significance between patients and controls”

7. Minor issues not for publication: please avoid abbreviations such as “i.e.” (line 2, page 10/26).
Response: Thanks for pointing this out. We have corrected it as requested.

EDITOR'S REQUEST:

Post-review copyediting: We recommend that you copyedit the paper to improve the style of written English.
Response: Thanks for your kind suggestion. We had asked two native-English speakers to correct some grammar mistakes to help it flow better.