Reviewer's report

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

Version: 2
Date: 5 October 2014

Reviewer: Gustavo Vazquez

Reviewer's report:

• This is an overall well written and designed meta-analytic study on the association between brain derived neurotrophic factor genetic polymorphism Val66Met and susceptibility to bipolar disorders. However, I have some minor comments for the authors below.

• 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?

• 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?

• 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

• 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

• 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.

• 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.
• Minor issues not for publication: please avoid abbreviations such as “i.e.” (line 2, page 10/26)

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no conflict of interests to report in relation with this review