Author’s response to reviews

Title: Evidence for Genetic Association of RORB with Bipolar Disorder

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Author’s response to reviews: see over
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To: The Editor, BMC Psychiatry

We are submitting a revised manuscript 204523254258777, McGrath et al. Evidence for Genetic Association of RORB with Bipolar Disorder, for consideration as an article in BMC Psychiatry. It describes our comprehensive work using a translational, focused approach to identify RORB as a candidate genes for bipolar disorder. We have made changes in response to the excellent suggestions from reviewers, as described below. We hope the paper is now acceptable for publication, and we would appreciate, if possible, an expedited review process.

Best regards,

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Reviewer 1 comments:
Abstract: Why not begin with the passage “Bipolar disorder in children and adolescents is characterized …”, and then refer to the clock gene-sections as this is in line with the rationale (clinical picture# molecular/genetic underpinnings).

The first sentence of the abstract has been edited to open with the clinical rationale.

Page 5: Why already summarize the key findings here? This would fit very well into the results/discussion section.

This section has been removed from the Introduction as requested

Page 9: The abbreviation AAO has already been explained before.

After removing the section mentioned above from the Introduction (p. 5), this mention on p. 9 is now the first use of the abbreviation of AAO, so the full explanation has been left.

Page 10, line 6: missing space bar.

This change has been made as requested.

Page 13: Perhaps the authors could discuss in more detail what could be possible reasons for the discrepant findings regarding the missing overlap of RORB SNPs from 3 GWAs with the present investigation.
A small discussion has been added.
Reviewer 2 comments:
Abstract
Authors should specify the extended form of the acronyms of the mentioned genes.

This change has been made as requested.

Introduction
Authors should start the introduction paragraph with a higher detailed description of bipolar disorder, specific features of bipolar disorders in pediatric patients and circadian rhythm abnormalities in bipolar disorder.

This has been added to the beginning of the Introduction.

At the end of the introduction the paragraph “After Bonferroni correction for multiple testing, we report positive associations between bipolar disorder and four intronic RORB SNPs and three RORB haplotype blocks in the case-control sample. We found no strong evidence for association between any RORA SNPs or haplotype blocks and bipolar disorder, nor do we saw evidence after Bonferroni correction for association between the age-at-onset (AAO) of bipolar disorder and any SNPs genotyped” should be removed because these are the results of the study and they should be described in the Results paragraph.

This change has been made as requested.

Materials and methods
Inclusion and exclusion criteria (age ranges, clinical diagnosis,...) should be better described for each group in a single comprehensive paragraph.

This is included in the last paragraph of the section titled Diagnostic Procedures

Sample identification
Authors wrote: “The first group of controls were ascertained from outpatients referred for routine physical examinations to pediatric medical clinics at each setting identified from their computerized records as not having ADHD and were found not to have BP-I on structured diagnostic interview”. What about other psychiatric diagnoses such as depression?

Other psychiatric disorders were not used as exclusion criteria. This has now been stated in the text.

Data analysis
Among statistical analyses power analysis should be performed.

We decided not to compute statistical power because that would require us to make assumptions about the unknown mode of inheritance and genotypic relative risk. Instead, we have discussed in the text the potential for low statistical power as a limitation of our work.

Results
Authors should report a table with the description of the sample in terms of socio-demographic and clinical variables.

These data are stated in the text of the Materials and Methods section.
Discussion


This study suggests there is indeed a high risk for false positive findings in studies that use a significance threshold of $\alpha = 0.05$. However, the study also states that using a Bonferroni correction is highly conservative and is therefore not likely to report many false positive results. As our study uses a Bonferroni correction, we think it more likely that any false positive results are created due to population stratification (as mentioned in the Discussion).