Reviewer's report

Title: Evidence for Genetic Association of RORB with Bipolar Disorder

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Reviewer: Alessandro Serretti

Reviewer's report:

The present paper is a genetic association study testing possible links between SNPs of both RAR-related orphan receptors alpha (RORA) and beta (RORB) genes in two pediatric bipolar sub-cohorts: a family-based sample of 153 trios (each trio consisting of an affected proband and both parents) and a case-control sample of 152 cases (all independent from the family-based samples) and 140 independent controls.

The strength of the study is represented by the high number of SNPs investigated in three different sample. Nevertheless, the writing is sometimes fragmented and it could be improved trying to logically connect each sentence and to consider the fact that the study should be higher attractive and comprehensible also to neophyte reader. Moreover, the risk of false positive finding considering the elevated number of SNPs investigated is extremely high.

The manuscript could be improved according to the following suggestions.

Major Compulsory Revisions

Abstract
Authors should specify the extended form of the acronyms of the mentioned genes.

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.

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.

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

Data analysis
Among statistical analyses power analysis should be performed.

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

Discussion

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
'I declare that I have no competing interests'