Reviewer's report

Title: Integrated Genome-wide Association, Coexpression Network, and Expression Single Nucleotide Polymorphism Analysis Identifies Novel Pathway in Allergic Rhinitis

Version: 3
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Reviewer: Jin Li

Reviewer's report:

The manuscript by Bunyavanich et al. presented an integrated genomics approach to identify genes and pathways associated with Allergic Rhinitis. They conducted GWAS across multiple ethnic groups, gene coexpression network, eSNP and pathway analysis. Their approach is of great value and interest to the field.

However, their conclusion needs additional supporting evidence.

Major:

1. asthma is a potential confounder in this study. Could the authors please indicate the percentage of asthma among their Allergic rhinitis cases and controls? and explain why they didn't include asthma status as a covariate in their association analysis?

2. For the genome wide significant SNPs shown in Figure S2, some do not have enough supporting evidence from neighboring SNPs in LD with them. As this is one of the important parts of their findings and the basis for other parts presented in the manuscript, further evidence is needed. A good validation method would be Taqman SNP genotyping assay. If this is not feasible to do, the authors please show the genome studio cluster plots of these SNPs in Figure S2.

3. The coexpression network was constructed based on gene expression data from the CAMP cohort, the samples of which were 100% from European Americans. However the GWAS loci (p<1x10^-6) were mainly from Latino population. It is known that gene expression varies between different ethnic groups. It is a limitation of the study. The authors please further expand discussion on this point.

Minor:

Did the authors take into account of imputation uncertainty when testing for association?

Please show the manhattan plot separately for study in each ethnic group and the meta-analysis for better viewing and comparison.

what is the genomic inflation factor of each individual GWAS?

The authors please check the meta-analysis p-value for SNP rs868688 presented in Table 2, as the p-value for each ethnic group is 0.49, 0.89 and 7.3E-07 and the meta-analysis p-value is 7.3E-07, which seems that two ethnic
specific studies have no weight in the met-analysis. This seems problematic and is not consistent with results of other SNPs presented in Table S2.

In Table S1, please indicate clearly what allele is presented?—risk allele or reference allele?

In Figure 3B, please show the gradation of color with the corresponding p-value range.

Please indicate the sample composition (the number of Allergic Rhinitis cases and controls in each ethnic specific study) in the stratified analyses according to asthma status.

**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.