Author’s response to reviews

Title: Integrative genomics analysis of various omics data and networks identify risk genes and variants vulnerable to childhood-onset asthma

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Author’s response to reviews:

Dear Editor and Reviewers:

We quite appreciate your favorite consideration and the reviewers’ insightful comments concerning our manuscript entitled "Integrative genomics analysis of various omics data and networks identify risk genes and variants vulnerable to childhood-onset asthma" (MGNM-D-20-00154). We have studied these comments seriously and have made corrections, which we hope meet with approval. Revised portions were marked in red color in the manuscript. We also responded point by point to each reviewer’s comments as listed below.

Point by point response to Editor’ and reviewer’s comments:
Reviewer reports:
Reviewer 1: 1. I agree that in the absence of individual-level data the sensitivity analysis is rather tough. But I would still encourage the authors to do colocalization analyses for multiple traits using proper GWAS summary statistics to give a sense as to which autoimmune diseases/phenotypes have nominal signals in or near the loci that seem to be associated to coA. There are quite fast summary colocalization techniques available. Also, I would strongly recommend performing a broad genetic correlation analysis (using summary statistics via LD score or others) to show which diseases in particular which autoimmune diseases are genetically correlated with coA. This coupled with the colocalization would give the reader a sense that there might be overlap between coA and other traits and facilitate the evaluation and interpretation of results. Also I wanted to point out that T1D, Rh. Arth are used as examples of autoimmune diseases. I would request the authors not to restrict their search to merely these mentioned diseases, but to broaden it up to a larger set of autoimmune diseases, whose GWAS summary statistics/results are available openly.
Answer: Thank you! As your kind suggestions, we selected six autoimmune diseases including type I diabetes, rheumatoid arthritis, multiple sclerosis, Crohn’s disease, Coeliac disease, and primary biliary cirrhosis with GWAS summary statistics from the UK-Biobank database to calculate the genetic correlations with childhood onset asthma by using LD score regression, and found there were non-significant LD regression scores between childhood onset asthma and six autoimmune diseases (Supplemental Table S13), which is in agreement with an earlier study on adult asthma and autoimmune diseases (Zhu et al. Nature Genetics 2018, 50(6):857-864). By performing a colocalization analysis using coloc R package, we found only a few of SNPs showed low or moderate posterior possibility between childhood onset asthma and six autoimmune diseases (Supplemental Table S14), suggesting that these identified association signals between risk genes and childhood-onset asthma not suffer remarkable influence from other autoimmune diseases. We have added some sentences in the Discussion section (See the second paragraph on Page 19 marked with red color).

2. My point about the null dataset is that it does not reflect the true null scenario. It reflects a null scenario where the underlying population prevalence is set to 0.5. This is not the true null scenario for the analysis. Merely restricting the analysis to a case-control sample with no true effect is not the appropriate hypothesis. The actual null that should be evaluated is when the underlying population prevalence is same as the prevalence of coA and there is no genetic effect on the coA status. In any case, I don't think the incorporation of dataset 2 adds value to the analysis since the majority of the analysis is based on a prior published GWAS and the validity/control for that is beyond the scope of this article.

Answer: Thanks for your kind suggestions! We have removed the analysis and other related contents on the null dataset.

Reviewer 2: I am satisfied with the revisions made, and deem this version of the manuscript acceptable.

Answer: Thank you!