Reviewer's report

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

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Reviewer's report:

The article by Ma et al. aims to disentangle the genetic susceptibility underlying childhood-onset asthma (coA) through integrative genomics approaches and bioinformatic analysis. The authors report a set of 31 genes, some being novel, to be associated to coA. Starting from a large-scale GWAS, they have underlined numerous independent analytic evidence that these genes might be associated to coA. The analyses approaches presented here are very thorough and authors are to credited for such well-designed follow-ups on various aspects by integrating numerous omics dataset and providing somewhat compelling evidence from several viewpoints. However, I have some concerns regarding the analysis:

1. It seems that most of the genes that the authors identify are somewhat related to autoimmune diseases. This is underlined in the follow-up gene-set analysis and enrichment analysis, where the autoimmune diseases show a strong enrichment. This raises the doubt that the initial premise of GWAS signals is somewhat questionable and requires further sensitivity analysis. It might be such that GWAS signals and subsequently the genes that are being identified are solely due to strong coheritability of coA with certain autoimmune diseases and hence the genes might not be pertaining to coA directly. It would be worthwhile to do a sensitivity analysis so give an idea how much the initial GWAS results pick up signals specific to coA. For example, within 13K coA cases assign those with autoimmune diseases (like T1D, Rh. Arth) as controls and rerun the analysis with reduced number of cases and enhanced number of controls. This will make sure that the signals being picked up are not solely due to coheritability and genetic sharing between traits. I understand there might be substantial loss of power due to the reduction in cases but such a sensitivity analysis is needed to ensure that coA specific variants/genes are being identified. Methods like SAIGE (Zhou et al.) might be handy for smaller case numbers.

2. In dataset, it seems the authors have assigned case control status randomly with probability 0.5. However, this needs to reflect the actual sample prevalence of the coA trait to be an acceptable control experiment. I think such analysis for only a modest number of samples like 1000G is difficult. As such, authors can also report the qq-plot, genomic control of the analysis to argue for proper false discovery control. I personally think the analysis of dataset 2 is unnecessary.

3. I am curious as to why the authors chose Sherlock over prediXcan or Fusion? Sherlock only compares the concordance of the peaks of the platforms being integrated where as the other methods can aggregate over the whole cis- region. I would be curious to see if in FUSION or predixcan analysis (with suitable reference panel of tissues) any tissue related to lung function shows up to carry signals. Currently the analysis restricts mostly to blood I believe?
4. There are a few minor typos in the article which needs to carefully checked again. Also I would request the authors to exercise greater caution while claiming "novel" findings. Since the link between asthma and autoimmune diseases is well known, so it would not be surprising to see such an enrichment of autoimmune related genes.

Lastly, I would like mention that, baring the few points above, the authors have really done a tremendous job in analyzing and following up the findings in one of the most comprehensive approaches.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
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Yes

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