Peer Review File

Article information: https://dx.doi.org/10.21037/tp-23-204

Reviewer A

1) First of all, the title is very arbitrary by using the term "key causative genes". The authors did not clearly and accurately define what "key causative genes" are but in their analysis, they only identified three genes that may be associated with childhood asthma, which is still very far from "key" and "causative". Please revise the title and elsewhere as appropriate to tone down this. The title also needs to indicate the research design of this study, i.e., a bioinformatics analysis.
   Reply: Thank you for your constructive comments. We have modified the title and corresponding parts in the text.
   Changes in the text: Title, all "key causative genes" in the text.

2) Second, the abstract needs some revisions. The background did not why the current bioinformatics analysis can help address the question of identifying key pathogenic genes of pediatric asthma. In the methods, the authors need to describe the variables and patient samples in the database used and how the "key" and "causative" genes were assessed. The conclusion on the "diagnosis of pediatric asthma patients" is not consistent with the focus of this study in the title "causative genes", so the authors did not clearly and accurately define the research questions to be answered by this study.
   Reply: Thank you for your constructive comments. We have made modifications to the abstract.
   Changes in the text: Paragraph 1,2,4/ Abstract.

3) Third, in the introduction of the main text, the authors need to review what has been known on the genetic biomarkers of childhood asthma, explain why it is difficult to identify key genes, have comments on the limitations and knowledge gaps of prior studies, and why the current bioinformatics analysis can address the limitations of prior studies. The authors did not explain what is "key causative genes" and it remains questionable the current analysis can identify "key causative genes".
   Reply: Thank you for your constructive comments. We have revised the introduction section and removed the inappropriate statement of key causative genes in the article.
   Changes in the text: Paragraph 1,2/ introduction.

4) Fourth, in the methodology of the main text, the authors need to briefly describe the research procedures and explain why the small patient sample in the database can answer the research question. The ROC analysis is used for assessing the diagnostic accuracy but diagnostic accuracy and identifying causative genes are two different things. The authors need to substantially revise the paper, even the research question was not appropriately defined.
   Reply: Thank you for your constructive comments. We have supplemented the selection of statistical methods for small sample studies in the methods. We have removed the erroneous

statements about key causative genes in the article and highlighted the importance of diagnostic genes in the research significance.
Changes in the text: Paragraph 1,2/ Methods.

Reviewer B

The paper titled “Screening of key causative genes for childhood asthma” is interesting, which sought to screen the key pathogenic genes of childhood asthma using a machine-learning algorithm based on transcriptome sequencing results. The authors conclude that the key pathogenic genes CXCL12, MMP9, and WNT2 in pediatric 43 asthma were identified by a bioinformatics analysis and machine-learning algorithm. The findings may guide the diagnosis of pediatric asthma patients, extend understandings of the molecular mechanisms of pediatric asthma, and lead to the development of new drugs. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) The author's analysis found that 118 genes were downregulated and 53 genes were upregulated. Why do all the discovered pathogenic genes happen to be up-regulated? Aren't the 118 down-regulated genes important? May I ask if there is any bias in the analysis method?

Reply: Thank you for your constructive comments. We strongly agree with your viewpoint that upregulating genes and downregulating genes are equally important. However, in our study, we selected the green module with the highest correlation coefficient with clinical traits. The green module is positively correlated with asthma traits, so the key genes are all upregulated genes. We supplemented the discussion.
Changes in the text: Paragraph 3/ Discussion.

2) The introduction part of this paper is not comprehensive enough. There have been many reports on asthma, and it is recommended to supplement them in the introduction, such as “J Thorac Dis 2023, 15(2):589-599; Ann Transl Med 2022, 10(24):1353.” It is recommended to quote these articles.

Reply: Thank you for your constructive comments. We supplemented “Ann Transl Med 2022, 10(24):1353” in the introduction. The research focus of this article "J Thorac Dis 2023, 15 (2): 589-599" is on chronic obstructive pulmonary disease, and we respectfully and cautiously believe that the citation may not be appropriate.
Changes in the text: Paragraph 1/ introduction.

3) The relationship between CXCL12 and asthma has been reported (Immunol Invest. 2022, 51(3):496-510), and it is recommended to supplement it in the introduction.

Reply: Thank you for your constructive comments. We supplemented it in the discussion section.
Changes in the text: Paragraph 3/ Discussion.

4) If the expression of CXCL12, MMP9, and WNT2 can be verified and tested in clinical cases, it may be more convincing.

Reply: Thank you for your constructive comments. This is the deficiency of this study, which we supplemented in the discussion.

Changes in the text: Paragraph 6/ Discussion.

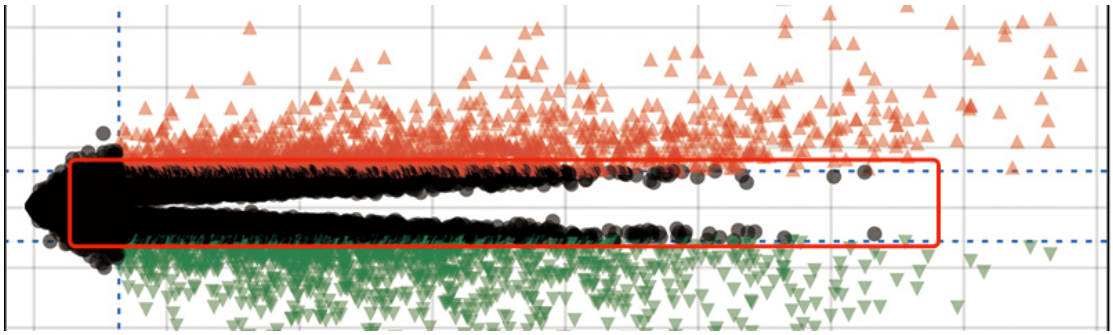
5) There are still some weak points in this paper. It is suggested that the author increase the possible mechanisms of CXCL12, MMP9, and WNT2 involvement in asthma. This is more conducive to support the conclusions of this study.

Reply: Thank you for your constructive comments. The lack of mechanism related research is a limitation of this study, and we supplemented it during the discussion.

Changes in the text: Paragraph 6/ Discussion.

Reviewer C

1. Figure 2: Please also define those black dots in the figure legends.

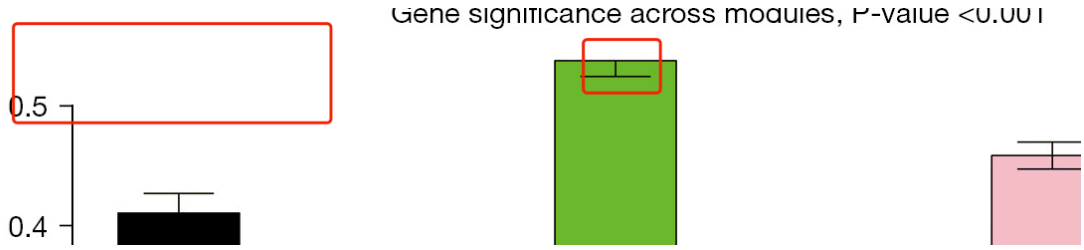


Re: Thanks for your comments, we have defined the black dot.

2. Figure 7

a. Please extend the Y-axis.

b. Please check if the green bar in the figure is complete.



Re: Thanks for your comments, we have revised figure 7.

3. Please define "***" in figure legend 10.

Re: Thank you for your opinion, we have defined "***".