Reviewer’s report

Title: A cis-eQTL allele regulating reduced expression of CHI3L1 is associated with late-onset adult asthma in Japanese cohorts

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Reviewer: Xingnan Li

Reviewer’s report:

In this study, Dr. Jun et al. performed a candidate gene study of CHI3L1, and indicated that the C allele of rs946261 may be associated with late-onset adult asthma through down-regulation of YKL-40 expression. Some of my concerns are:

Major:

(1) The organization of the manuscript is not clear, sometimes confusing. For example, (a) In the Materials and methods section (Page 9, Lines 140-144): 'Thus, we first searched the GTEx Portal database,......, (Table 1: Figure 1)'. The results of these 34 SNPs and/or 6 SNPs (Table 1 and Figure 1) should belong to Results section. (b) In the Materials and methods section (Page 11-12, Lines 182-199): 'We performed a two-step cluster analysis,......". Is this cluster analysis performed in this study or previously? If it is done previously, this part should go to Introduction section. If it is done currently, then it should go to Results section.

(2) The association results of 6 SNPs should be shown in the Table 1.

(3) The association of rs946261 with asthma is not convincing without other evidence, such as the findings from previously published large sample size GWAS. On the basis of previous studies, the association of SNPs in CHI3L1 with asthma has never been confirmed, at most the association is very weak and inconsistent. It needs to be carefully discussed.

(4) Reference #5 and #6 both indicated higher levels of YKL-40 were correlated with asthma and asthma severity. In this study, lower CHI3L1 mRNA was correlated with asthma. How to explain this contradiction?

(5) The function of CHI3L1 is not clear or it has multiple potential function. The conclusion of inflammasome activation is far-reaching and needs to be weakened.

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?
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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