Reviewer’s report

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

Version: 0 Date: 21 Dec 2018

Reviewer: Erik Fransen

Reviewer’s report:

The authors carried out a case-control into the genetic causes of asthma. They found one variant in the promotor of the CHI3L1, previously known to influence the expression of the downstream gene, to be associated with asthma risk. A survival analysis showed a significant association between the genotype and age-at-onset. When partitioning the asthma cases into six subgroups, according to phenotype, the variants in the CHI3L1 promotor showed a significant association to one of the six clusters.

I am not a specialist on the asthma phenotype, so I did not revise that part of the manuscript. However, as a statistician and genetic epidemiologist, I noticed several methodological issues, which make reported associations are not convincing.

Major comment:

My main concern is the total lack of correction for multiple testing. The genotyping was carried out through a GWAS, which gives data on about 4 million markers. One SNP was picked out - rs946261 in the promotor of CHI3L1, with a p-value for association with asthma of 0.018. There are - by definition - 1.8 percent of all SNPs reaching that p-value under the null hypothesis of no association. Even in the total absence of any genuine association, hundred thousands of SNPs are expected to reach a p-value of 0.018. The fact that the SNP is a known e-QTL, does not add to the argumentation that the SNP has an effect on disease risk. Neither does the possible functional role of CHI3L1 provide any additional proof - many genes are involved in the asthma pathophysiology.

Minor comment:

The association test between the genotype and the disease status was reported with a one-sided p-value. A one-sided test starts from the null hypothesis that one allele (the putatively deleterious allele) leads to an improvement of the disease status. This does not make sense in the present situation - here one should start from the null hypothesis of no association between the allele and the disease status. The association test should be carried out using a two-sided test.

The partitioning of the patients into clusters is poorly explained and argued. On line 180-181 the authors mention previously determined subgroups of patients, but no reference is provided. A
model to partition patients into subgroups is built using a classification and regression tree (CART) model, using a set of 880 adult patients of which no details are provided. They seem to be not part of the current genotyping study, but no descriptive statistics are given. It is highly unclear if this cohort is matched to the collection 971 genotyped individuals. The CART model is then used to classify the 971 individuals into the six groups.

The output of the multinomial regression is confusing. In a multinomial regression with a six-level outcome, one of the outcome levels has to be the reference level. The effect sizes (odds ratios) are then referred to that reference level - the odds ratio of a non-reference level equals the odds of the non-reference level, divided by the odds of the reference level. Here, we see six odds ratios, each of which with a p-value. Was the control group included in the analysis as a seventh group, and used a reference? Assuming this latter scenario do the p-values represent the null hypothesis that the odds ratio (with the control group) equals 1? In this latter case, you need to adjust for multiple testing.

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

No

**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

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:
1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal