Reviewer's report

Title: Effects of Endotoxin Exposure on Childhood Asthma Risk are Modified by a Genetic Polymorphism in ACAA1

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Reviewer: Erik Melen

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Review comments to Sordillo et al 'Effects of Endotoxin Exposure on Childhood Asthma Risk are Modified by a Genetic Polymorphism in ACAA1'

The authors have investigated potential GxE interactions in relation to asthma and eczema using 7 previously associated SNPs and endotoxin exposure as interaction variables. Data from two rather similar “high-risk” asthma studies in Massachusetts and Connecticut, USA were pooled and analyzed together. The main finding is that the protective effect of early endotoxin exposure on asthma may be dependent on a particular SNP in ACAA1. This gene resides nearby a TLR signaling gene, MYD88, but it is not clear if the ACAA1 gene is directly involved in endotoxin-related pathways, or if an effect is mediated via e.g. MYD88.

The paper is clearly written with a well defined hypothesis, and adequate statistical methods have been used. The main limitations with the study are rather small sample size, no replication study and no functional data to support the ACAA1 findings. Nevertheless, the study reports novel, interesting data that add to the current literature that genes and environment act together on asthma development, and that these interactions likely play an important role.

Major compulsory revisions:

1) Sample size must be considered a rather limited factor since only 95 asthma cases and 196 ctrls (from the two studies) are included in the final analyses. This is also reflected by the fact that despite a very significant p=0.003 for interaction between exposure and rs156265 for asthma, the OR fails to be significant in individuals with at least one copy of the minor allele (95%CI 0.15-1.04). Sample size has discussed to some extent, but it needs to be underlined that this is a rather small study after all.

2) How were the 95 cases and 196 ctrls selected from the original 505 infants in the Boston study and 1002 families in the Yale study? This is a very small subset of the original study participants and the selection process must be described in more detail. Risk of selection bias? Also, it might be worthwhile to point of that these studies are “high-risk” since inclusion criteria included one parent or one older sibling with asthma or allergy. Does this affect the possibility to generalize the results to a broader population?
3) Asthma was defined as parental report of doctor’s diagnosis during first 6 y of life. This is a well established definition, albeit rather unspecific (many early wheezers may be included). Total IgE was also measured but no interaction was found related to this outcome. Since endotoxin exposure also has been associated with reduced risk of atopy, it would be valuable to see interaction results also for specific allergic sensitization (I assume these data are available in the studies).

4) Adjustments were done for maternal asthma, day care, income and breastfeeding. How were these potential confounders selected? Adjustment for exposure to passive smoking? Sex? Boys seem to have higher asthma risk.

5) I assume CD14 genotypes are available in these studies as reported in Litonjua, JACI 2005? Are CD14-exodoxin interaction analyses significant in these studies? Although the CD14 SNPs fall outside the inclusion criteria for SNP selection here (associated with asthma or eczema as presented in Sharma et al, submitted), it would be valuable to see if one of the most replicated GxE interactions in the asthma-allergy field (CD14-endotoxin) can be observed also in this study. Replication must be considered gold standard not only in genetic association studies, but also in interaction studies. Thus, replication and validation of GxE interaction results, as well as meta-analyses, are needed in this field.

Minor essential comments

1) Figure 2 and 3, please add 95% CI to the asthma frequency numbers to get an estimation of the precision of each point estimate.

Discretionary Revisions

1) In the Abstract, Results, I recommend to delete “term”, leaving only “(p=0.003 for interaction)”

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.