Reviewer’s report

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

Version: 1  Date: 17 August 2011

Reviewer: Erick Forno

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GENERAL COMMENTS:
This is an interesting paper with results that contribute to the knowledge base in the subject. The authors report a polymorphism in gene ACAA1 that modifies the effect of endotoxin exposure on the risk of asthma: exposure to increasing levels of endotoxin was protective for asthma in subjects with the polymorphism, but not in those without.

One significant drawback is the lack of a replication population. However the authors clearly mention such limitation in their discussion. Further studies will be required to confirm these findings, as well as to elucidate the potential role of gene ACAA1 in asthma-related pathways.

MINOR ESSENTIAL REVISIONS:

1) Methods: Multivariate regression was adjusted for several covariates. However "cohort" was not one of the covariates listed in the adjusted models, and should be included. Authors state in their results that "the effect of cohort did not alter the observed interaction"; therefore including it in the models should not alter the results.

2) Figures should be numbered in the order they appear in the text. Currently fig.2 is referenced first and should become Figure 1. The current figure 1 should become Figure 2 (furthermore, figures 1 and 3 could become Figure 2A and 2B, since both depict LD plots for the same two SNP).

3) Table 1: While subjects were all enrolled within a relatively narrow time period and should therefore be all of similar age, "Age" should be included in the baseline characteristics of the cohort.

4) I did not see mentioned how many cases and controls come from each of the cohorts. It should be stated. This could explain why (in the stratified analysis in Supplemental Table 4) the Yale cohort shows a much more pronounced "protective" OR and a significant interaction value, whereas the Home Allergens cohort does not.

Level of interest: An article whose findings are important to those with closely related research interests
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.