Reviewer's report

Title: ITGB5 and AGFG1 Variants are Associated with Severity of Airway Responsiveness in Asthma Subjects

Version: 1 Date: 12 February 2013

Reviewer: Muhammad Towhid Salam

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General comments:

Although there are heterogeneity (in population characteristics and outcome assessment) across the discovery and the replication samples (possibly an unavoidable situation for GWAS), the paper is well written and may add to the growing body of literature on the genetic determinants of airway hyperresponsiveness (AHR). While the authors have put together a strong collaborative group, the inherent limitation of the study design reduced the enthusiasm of the study findings. While some study design limitation cannot be overcome, the authors could conduct some sensitivity analyses to indirectly examine the influence of subject characteristics and the robustness of the study findings.

Major compulsory revisions:

1. The major limitation is the heterogeneity by age, asthma status and smoking history among the discovery and replication samples. While the discovery population includes asthmatic children, replication samples were not children. Although the DAG study was conducted among adult asthmatics, the LHS study included adult smokers and excluded subjects who were not using asthma medications regularly. As the authors pointed out, these heterogeneity may have influenced the replication finding. Suggest that the author conduct a sensitivity study among non-smoking DAG subjects to find out whether they could replicate the findings.

2. Given the lung-function distribution, it appears that some of the LHS study subjects may have met the criteria for COPD. Also, some LHS subjects required a very high-dose of methacholine to elicit AHR, which is beyond the distribution of LnPC20 is the discovery sample. It will be useful to conduct another sensitivity analysis by restricting the replication in LHS subjects who did not have COPD and had similar distribution of LnPC20 as that of the discovery sample.

Minor essential revision:

1. Include asthma and COPD status in Table 1 (since it appears that some asthmatics and COPD cases might be in the LHS study).

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.