Reviewer's report

Title: SNP-Set Analysis Replicates Acute Lung Injury Genetic Risk Factors

Version: 2 Date: 24 March 2012

Reviewer: Guruprasad Aithal

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This is a case-control genetic association study using linkage disequilibrium block to replicate previously described associations with acute lung injury in a prospective cohort of trauma patients who belonged to two different ancestries.

Major Compulsory Revisions:

Introduction:
Page 4: ‘In addition, SNP-set analysis can potentially evaluate epistatic effects, or interactions between groups of SNPs.’ Please elaborate on this point including how epistasis and hypostasis will influence genetic susceptibility. Please also provide examples/ references to support this statement.

Methods:
Candidate gene selection: It will be helpful to demonstrate in a ‘consort diagram’, the process of how they started with a long list of published associations, criteria for selection or exclusions and the final list of candidate genes that they eventually included in the investigation.

Page 9: ‘We used identical-by-state (IBS) and quadratic kernels, as defined below in equations (1 – 3), to allow the incorporation of complex and epistatic effects among SNPs in a set.’ Please clarify whether hypostatic effects were also considered; if not why not?

Page 9: ‘The quadratic kernel has the additional feature of incorporating all two-way interactions and quadratic main effects of the SNP set on the ALI phenotype.’ Please clarify the difference between ‘severity of ALI’ vs. ‘phenotype of ALI’.

Power Calculation: I suggest that authors clarify the purpose of power calculation. From what I see that the size of the sample was determined by the number patients admitted with this condition (trauma) to intensive care in the hospitals that were enrolling patients for the study. If this is true then the power calculation is only intended to estimate what is the range of relative risks the given sample size able to detect. There no such clarity in the manuscript at present. In addition, there were at least two different ancestries within the cohort which hasn’t been taken into consideration. The ratio between cases and controls will also affect the power calculation. All these need to be clarified.

Discussion: There is just a mention in the discussion regarding the relevance of
associations that the study has confirmed and its’ relationship with the clinical phenotype. While the study appears to have confirmed ALI associations with IL6, IL10, IRAK3, VEGFA among African American trauma subjects, and with VEGFA and NFKBIA among European Americans, it would be important to discuss in detail whether there were any similarities or differences in the clinical phenotypes (in terms of severity or ALI or aetiology leading to ALI) between the cases included in the current study and those which were included in the previous studies where similar associations have been reported.

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

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.