Reviewer's report

Title: Genetic variations in the TIRAP gene are associated with increased risk of sepsis-associated acute lung injury

Version: 1 Date: 4 August 2010

Reviewer: Chiea Khor

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Zhenju Song and co-authors describe a genetic study on Mal/TIRAP, a bridging adaptor molecule downstream of TLR2 and TLR4 signalling. They assessed a total of 5 single nucleotide polymorphisms (SNPs) of varying allele frequency in a longitudinal cohort comprising individuals of Han Chinese descent, and found suggestive evidence (univariate P = 10^{-3} to 10^{-4}) of association with acute lung injury for two out of the 5 mutations. Of note, the 3 study groups for comparison appear to be well matched.

Minor comments:

1. The value of the study would be greatly enhanced with the inclusion of a replication sample set; I would indeed recommend this inclusion if the authors have a replication set which is forthcoming. However, I am very mindful of the difficulty in assembling longitudinal cohorts of this nature, where individuals with acute lung injury + sepsis, sepsis per-se, and controls are carefully matched for potential confounders.

2. As single-point P-values are actually more significant than the haplotype P's, may I suggest dropping the haplotype analysis altogether, as it adds very little to the results. Also, haplotype analysis using unrelated (e.g. in a case-control study) individuals could be unreliable, as they are produced using computer algorithms. To be able to discuss haplotypes meaningfully, a family-based cohort should be included and direct, vertical transmission of the haplotypes tested.

3. For figure 1, as the authors elect to report the r-squared coefficient to reflect LD, may I suggest that they change the colouring of the diamonds to reflect the r-squared scale on haploview? Currently, the colour scheme chosen is indicative of the D-prime scale.

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:
Yes, I was an author on one of the early papers on Mal/TIRAP (specifically describing the S180L mutation) which the authors are currently citing.