Reviewer's report

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

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Reviewer: Thomas Hawn

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This study examines where polymorphisms in Mal/TIRP are associated with ALI or sepsis in China. The main finding of the association of 2 TIRAP SNPs with ALI is novel and adds to the literature on disease associations of polymorphisms in this gene. The strengths of the paper are a well-defined case group of the same ethnicity with convincing and statistically associations for the primary endpoints. Weaknesses include unclear rationale and detail for the adjusted analysis and the haplotype analysis.

Major Compulsory Revisions:

1. The main finding is that 2 SNPs (rs595209 and rs8177375) are associated with ALI when compared to healthy controls or sepsis alone patients. The unadjusted data are convincing with statistically significant differences. The rationale and details for the adjusted analysis are not well articulated. The data is adjusted for age, gender, BMI, APACHE score, diabetes, liver cirrhosis, and smoking history. Several questions need to be addressed to clarify this analysis:
   A. what is the rational for choosing these 7 variables? Although age and gender are commonly done, the others are not. Are the other 5 variables recognized as established risk factors for ALI? Given that none of these variables had a different frequency among the 3 groups (table 1), the rational for adjusting is further questioned. B. By definition, the healthy controls have no history of diabetes, cirrhosis, or APACHE scores. These variables cannot be adjusted for when comparing ALI to controls.

2. Haplotype analysis: A 2 SNP haplotype analysis is performed on rs595209 and rs3802813. The rationale for selecting these 2 SNPs is not clear since they have the highest r-squared value of all of the 5 SNPs. A more informative analysis would be to do a 2 SNP haplotype of rs595209 and rs8177375. These are the 2 SNPs associated in a single SNP analysis and they have an r-squared of 0.17—so there is potential to have independent effects that would be further illuminated with a haplotype analysis. The current haplotype analysis could be replaced with anrs595209-rs8177375 analysis.

Minor essential revisions:

1. Case definition: The definitions based on consensus guidelines are appropriate. A brief summary of the details would be helpful.

2. Healthy controls: More details would be helpful. Where were these individuals enrolled? Community, outpatient clinic, inpatient setting? Were they given a
health history questionnaire? They have no “recent acute illness or any chronic illness …” Do any have a history of a serious acute illness? It seems unlikely that they could have a history of ALI or sepsis due to the low frequency of these conditions—but it also appears that the case definition would not exclude this possibility. Further details would help clarify this.

3. Table 3: The Bonferroni correction notation in the table footnote is not clearly annotated. Which SNPs remain significant after correction?

Minor discretionary revisions
1. Tables 2 and 3 could be combined to save space.

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

**Quality of written English:** Needs some language corrections before being published

**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