Reviewer's report

Title: Associations between interleukin-1 gene polymorphisms and sepsis risk: a meta-analysis

Version: 1 Date: 27 September 2013

Reviewer: valentina mangano

Reviewer's report:

The manuscript by Zhang and colleagues describes a meta-analysis of studies investigating the association between polymorphisms in the IL-1 gene cluster and the risk of sepsis, with the aim of summarizing existing evidence and drawing general conclusions. The work is of interest to those working in the field of genetic susceptibility to sepsis, although it presents some important limitations, which are in part acknowledged by the authors.

Major Compulsory Revisions

- Writing
  I would recommend the authors to thoroughly edit the manuscript to improve the quality of English.

- Design and analysis
  Eligibility of articles for the meta-analysis was not based on the quality of the research, for example an appropriate source of controls in case-control studies. I reckon this is one of the major limitations of the manuscript and I encourage the authors to address it. I am not familiar with the Newcastle-Ottawa method for quality assessment, but the authors state that studies with a score of 7 or higher are considered of high quality, and then include in the meta-analysis studies with lower scores. The authors should please correct or justify this inconsistency.

  The threshold for significance has been set by the authors as equal to 0.05. Please avoid expressions as "slight significant association" or similar for results where p-value is larger than 0.05. If you reckon the result is anyhow noteworthy, please describe the apparent effect of the polymorphism but clearly stating that it did not reach statistical significance.

  I would suggest to use a random effect method whether or not heterogeneity exists, so that results can be interpreted in an homogenous way (estimates from random and fixed effect methods have different meanings).

  It would be helpful to include forest plots showing ORs and their 95% CI for the individual studies, so that heterogeneity can be visually assessed. To add useful information, the size of boxes for ORs should be proportional to the weight of the study in the meta-analysis.

  Please further investigate and describe the potential sources of heterogeneity. In
particular, the relevance of the different genetic background of the populations included in the analysis should be stressed. Furthermore, one important source of heterogeneity might well be the different source of controls. Please also conduct meta-regression with covariates for all polymorphisms and show the results (perhaps as supplementary material).

Please show the results of sensitivity analysis (also as supplementary material).

- Introduction
Please briefly describe sepsis. Is it also important that more references are given to support the authors' statements (e.g. the role of IL-1#, IL-1# and IL-1ra in sepsis).

- Discussion
More references should be given to support the authors' statements (e.g. on the role of IL-1#).

Minor Essential Revisions

Please use capital letters when then using an abbreviation (e.g. Single Nucleotide Polymorphism and SNP) and use italics when referring to genes and polymorphisms. Please make sure that alleles are named consistently throughout the text.

- Abstract
I would find it useful to show rs identification numbers in the abstract.

I suggest the results of association analysis for each polymorphism to be presented in the same order as they are presented.

Please try to clarify and synthesize further the results for IL-1RN VNTR. Is it not always stated what alleles/genotypes are compared and whether the results are that of the analysis in the overall population or of subgroup analysis. Individuals carrying the 2 allele should always be of genotype 2/2 and L/2.

- Introduction
Please change "Genes containing IL-1A..." to "IL-1A...loci" or similar. I would also omit the sentence "The genes of IL-1 complex are polymorphic" as virtually all genes are.

- Materials and methods
Please be more specific and indicate what kind of bias you aimed to minimize.

Please include the data collection form as supplementary material.

- Results
Please try to further synthesize the results, for example describing only those for the genetic model that showed the stronger association and not for all genetic models.
**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:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.