Reviewer’s report

Title: Host genetic variability and pneumococcal disease - A systematic review and meta-analysis

Version: 0 Date: 10 Jun 2019

Reviewer: Mohammad Reza Jabal Ameli Forooshani

Reviewer’s report:

Kloek et al. provided a comprehensive and well-written meta-analysis of host genetic variability in the context of pneumococcal meningitis. Through an in-depth analysis of published literature during the past 35 years (1983-2018), they have demonstrated that the majority of identified genetic variants are found in genes involved in host immune response to microbes. Based on their meta-analysis, they identified that variants on CD14 and MBL2 genes significantly associate with pneumococcal disease.

The manuscript follows a structured and detailed review of association signals involved in individual components of the host immune system. The method section thoroughly addresses the potential concerns regarding the aggregation of data from diverse resources and Importantly, the limitations of their meta-analysis are adequately discussed in the final section. Nevertheless, there are few comments that if adequately addressed will increase the readability of the paper and addresses minor scientific flaws.

Comments:

1. Figure 1 resolution does not meet the standard requirement of a high-quality paper. Please consider providing a high-resolution figure according to the journal instructions.

2. In multiple occasions, authors referred to association studies that carried out on white patients (for example page 4, line 46). Although colloquially correct, the term "White" does not appropriately indicate a specific ethnicity. Please consider replacing it with more appropriate terms such as "Caucasians" or "European descendant" patients.

3. PCR is a molecular technique for amplification of target sequences and it does not reveal the genotype unless coupled with other molecular methods such as RFLP. Hence the use of PCR for determining genotypes (Page 5, line 12 & page 13, line 22) is not correct. Provide the correct method used for genotyping of the patients.

4. Tables in figure 2 (Forest plots derived from meta-analysis) are not consistent. Some tables have an extra column indicating the year of the study while the year column from other tables missing.
5. Please consider using figure sub-legends for figure 2 and reference to the relevant plot in the "candidate gene approach" section.

6. Page 6- line 46 "In the meta-analysis…": Please consider using appropriate punctuations in a compound/complex sentence.

7. Figure 3- Please add the takeaway message from the funnel plot before listing abbreviations.

8. Please add HGVS representation of the SNPs to the figure legends: for example; rs1800450 (NM_000242.2(MBL2):c.161G>A (p.Gly54Asp).

9. Please correct the typo in the spelling of word "independent" in line 12, page 13.

10. A significant association signal does not imply a causal relationship and in fact, due to LD, the causal allele might be up to few Kbp apart from the association signal. Identification of the causal allele requires the application of fine-mapping methods. Please consider paraphrasing the last sentence in line 48 of page 12 to reflect the correct scientific inference from the mentioned results.

11. Please consider including a paragraph in the discussion section of the paper reflecting on the availability of low-cost high-throughput sequencing in the clinic and its implication on the susceptibility gene finding and improved diagnosis of patients at risk.

Overall, I believe the current manuscript is a timely and well-written review of susceptibility genes in the context of pneumococcal disease and will attract the attention of experts in the field. Provided that authors adequately address the aforementioned comments, I recommend this paper for publication.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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