Reviewer's report

**Title:** Addition of host genetic variants in a prediction rule for post meningitis hearing loss in childhood: a model updating study

**Version:** 1 **Date:** 25 January 2013

**Reviewer:** Matthias Klein

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In this study, SNPs of 11 genes involved in pathogen recognition were measured in 471 children with bacterial meningitis (causative pathogens S. pneumonia and N. meningitides) and the data were added to a clinical prediction model for hearing loss complicating bacterial meningitis. The prediction model that was used has previously been published by the same group (Koomen et al., Pediatrics 2003). The addition of SNPs of the TLR9 gene or in the TLR2 and TLR4 genes to the prediction model led to an increase of AUCs of the model from 0.856 to 0.861 and 0.856 to 0.875, respectively, which did not reach statistical significance (p=0.570 and 0.335, respectively). The authors argue that although the effect was negative, further study on the inclusion of SNPs in prediction models should be ongoing.

The authors took the effort and tried to incorporate genetic factors that have been shown to be relevant for the immunopathogenesis of hearing loss as a complication of bacterial meningitis. Although this was a negative study, the approach is quite interesting. However, there are some factors that need to be considered.

**Major revisions:**

(i) Have the authors thought about the possibility that certain SNPs might have influenced or been associated with clinical parameters that were included in the initial prediction model (like CSF glucose levels or causative pathogens)? An association between the investigated SNPs and clinical points of the prediction model might explain the lacking effect when SNPs were added to the model.

(ii) It is important to notice that hearing loss especially occurs in patients with pneumococcal meningitis and less frequently in patients with meningococcal meningitis. E.g. in a recently study work by the same authors, hearing loss was found in 4% of children with N. meningitides meningitis and in 21% of patients with S. pneumoniae meningitis. Furthermore, data on the immunological relevance of the selected SNPs in meningitis were mainly obtained in animal models of pneumococcal meningitis or, for N. meningitides, come from in vitro studies only. As N. meningitides was the main causative pathogen in the patient cohort used here (391 cases = 83%), etiology of meningitis might be a relevant factor for the outcome of the study that needs to be discussed.

**Minor revisions:**
(i) The authors write that “Genetic factors contribute to a good prediction model” in the abstract of the manuscript. How can this be derived from the study? The same is true for the statement “This study shows us the direction that studies including genetic predictors should be going”. The authors seem very optimistic on the value of genetic factors as variables in a prediction model. Given the negative results of the study, it is unclear what this optimism is based on. Furthermore, SNPs are not available during routine clinical practice. As no direct treatment decision can be derived from this information and most health care systems have to deal with financial problems already, it is unlikely that this will change in the near future. Thus, it should be discussed that the clinical applicability of the published approached, namely to include SNPs in a prediction model, remains critical. However, although a clinical application of the approach to include SNPs into a prediction model may still be far from clinical use, the question arises whether prediction models might be useful in the assessment of a possible pathophysiological relevance of SNPs in certain diseases.

(ii) As p-values were far from being significant, the authors should avoid writing that AUCs “increased” when SNPs or a combination of SNPs were included.

Discretionary Revisions

(i) The paragraph on a pathogenetic function of TLRs and MyD88 in the discussion section can be omitted.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**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.