Author's response to reviews

Title: Nitric oxide synthase 2A (NOS2A) polymorphisms are not associated with invasive pneumococcal disease

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Version: 2 Date: 4 March 2009

Author's response to reviews: see over
05 March 2009

Dear Editor

**Nitric oxide synthase 2A (NOS2A) polymorphisms are not associated with invasive pneumococcal disease MS: 1557160036252989.**

Thank you for giving us the opportunity to revise and improve our manuscript. Please find below a point-by-point response to the reviewer’s comments.

**Reviewer’s report**

**Title:** Nitric oxide synthase 2A (NOS2A) polymorphisms are not associated with invasive pneumococcal disease  
**Version:** 1 **Date:** 17 February 2009  
**Reviewer:** Stephen J Chapman

**Reviewer’s report:**

Major Compulsory Revisions
1. Nil

Minor Essential Revisions
2. Spelling of ‘asymptomatic’ in abstract, background.  
   Corrected
3. Background, second paragraph, reference 10 in fact describes an association between IPD and members of the ‘inhibitor of NF-kappaB’ family NFKBIA and NFKBIE, not NF-kappaB itself.  
   Corrected
4. Table 2, ‘95% CI’ – presumably of odds ratios?  
   This is the 95% CI for the regression coefficient

Discretionary Revisions
5. Table 2, the genotypes presented appear to pool the cases and controls and survivors/non-survivors for each snp, might be more informative if presented these separately. The MAFs for cases and controls in table 1 allow easy comparison.  
   This has been modified.
6. Case definition. Some experts would not consider pneumococcal pneumonia in the absence of bacteraemia to be ‘invasive pneumococcal disease’, the authors may wish to expand upon this – although I appreciate that in the very least the phenotypes are very closely related and the distinction may simply reflect blood culture practice or timing. In any case it is highly unlikely to alter the conclusions of the paper.

We agree that this definition is potentially controversial, so we have now included a few sentences. “Of the 41 cases with pneumococcal pneumonia, 13 (32%) were bacteraemic by blood culture or PCR and 31 (78%) were positive by PCR of lung aspirate. As the majority of patients with pneumococcal pneumonia do not have bacteraemia, we did not make this a requirement to fulfill the criteria of invasive pneumococcal disease.”

Conclusions

7. A comprehensive and well-written assessment of a biologically plausible candidate gene for IPD susceptibility and outcome. Although a negative study, it is well-designed and executed and draws appropriate conclusions. As such the study adds to the overall body of knowledge on this subject and I would recommend publication.

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

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

Reviewer’s report

Title: Nitric oxide synthase 2A (NOS2A) polymorphisms are not associated with invasive pneumococcal disease

Version: 1 Date: 23 February 2009

Reviewer: Elena Urcelay

Reviewer’s report:

The manuscript reports a tagging study of polymorphisms in the NOS2A gene associated with invasive pneumococcal disease susceptibility in Malawi. Given the functionality of the gene, this is an interesting and clearly written study. A trend for association was observed in one of the genotyped SNPs. However, the presentation of data in Table 2 could be clearer, including the frequencies (%) of the minor allele in cases and in controls in addition to the n. Are allele frequencies or homozygous wt individuals listed?

This has been modified.

Minor comments: correct the following typos: asymptomatic (abstract), principal (1st line in background).

Corrected.

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

I trust that you will be satisfied with the amendments.

With kind regards

Dr Enitan Carrol

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