Reviewer's report

Title: Lack of association between polymorphisms of the IL18R1 and IL18RAP genes and cardiovascular risk: the MORGAM Project

Version: 2  Date: 22 December 2008

Reviewer: Bernard Keavney

Reviewer's report:

No major compulsory revisions: this seems to be a scientifically valid and correctly interpreted negative study.

Minor essential revisions:

Please indicate quantitatively the contribution of the current work in context of previous investigations of polymorphisms in these genes. Previous study of these genes in the AtheroGene project is mentioned in passing, but no detail is given. It's not clear at the moment from the manuscript exactly what this study has added to the existing literature.

Odds ratios and confidence intervals have not been provided for the SNP-by-SNP analyses. Please provide these to give some indication of the uncertainty remaining after this potentially important negative study.

It is not clear what the strategy was for the testing of SNP X SNP X Covariate interactions. Please describe this in more detail. For instance, was each IL-18 SNP tested with each SNP in either of the receptor constituent genes? Or was each SNP in each gene tested in combination with every other SNP? Some comment on the power of the study to detect the interactions that were sought would be appropriate. It is not likely that there was much power to detect third order interactions.

What was the rationale for including both haemorrhagic and ischemic stroke in the case group?

Discretionary Revisions

The statement about Hardy-Weinberg equilibrium in the IL18R1 gene is confusing and seems contradictory. A supplementary table of those SNPs that failed HWE at p<0.01 might be more informative.

A statement on how the allele frequencies at typed SNPs compared with the HapMap frequencies would be helpful.

I found the description of the case-cohort design somewhat difficult to follow in the text. If I have understood it correctly, an age-stratified subcohort was randomly selected from each study, which as expected was mostly made up of controls. Additional cases were then selected from the remainder of the study
population in each cohort. Were these all available cases or was there any additional selection (younger age, for example)? I also suggest simplifying Table 1 by removing the first two columns.

Why are some numbers in Table 2 in italics?

I suggest the use of rs numbers throughout the manuscript to identify SNPs.

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