Reviewer's report

Title: Association between variations in the TLR4 gene and incident type 2 diabetes is modified by the ratio of total cholesterol to HDL-cholesterol

Version: 1 Date: 11 October 2007

Reviewer: Colin Palmer

Reviewer's report:

General: This is an interesting hypothesis generating exercise, which has explored the effect of haplotypic structure of TLR4 on type 2 diabetes incidence, with a view to an interaction with TC/HDL ratio. The authors report that the interaction term works between different SNPs/haplotypes in men and women. Indeed many apparently significant observations are reported, far greater than would be expected by chance (as confirmed by their Bonferroni correction). However the picture is really muddled particularly by the gender issue. At no point in the manuscript is the idea of testing for a three way interaction between gender/genotype/ and TC/HDL. This would probably be the best way forward in a regression model with the different haplotypes. It is clear that there are similarities in the observations between men and women as well as dissimilarities in this analysis, and that many of the comparisons rely on incredibly small sample groups, which will provide very volatile results. It may be that the gender issue is a red herring.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

I would prefer to see the whole analysis run on the joint gender group, with gender in as an interacting factor and as a covariate. I also think that performing a step wise modelling of combinations of the variants in regression models may help refine the genetic model.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests