Reviewer’s report

Title: IL6 and CRP haplotypes are associated with COPD risk and systemic inflammation: a case-control study

Version: 1 Date: 6 November 2008

Reviewer: Jemma Wilk

Reviewer’s report:

The authors have evaluated association between SNPs and haplotypes in 3 genes (CRP, IL6, and FGB) with COPD, the corresponding biomarkers, and COPD-related phenotypes. They have produced a nicely written paper with interesting findings.

Major Compulsory Revisions:

1) There is some discordance between the statements made in the methods/results and the presentation in the tables. The authors indicate that COPD and the 3 measured systemic inflammation levels were treated as 4 primary outcomes. However, in both Table 5 and Table S5, there are results labeled as “Not tested”. The authors appear to have tested IL6 SNPs and haplotypes against all 4 outcomes, but CRP and FGB is only tested against COPD and the corresponding biomarker. The rationale for this is unclear.

2) On page 10, the authors indicate they “calculated haplotype-specific scores and then estimated haplotype effects…”, but it would appear that they only performed haplotype-specific analysis when the global haplotype test achieved a p-value < 0.1, which is quite reasonable. If this is correct, then that should be stated. If this is the rationale, then it would appear that the CRP haplotype-specific analyses should be performed for the phenotype Maximum workload, watts (Table 8).

3) The authors should discuss the limitations of their FGB analysis and results given the failure of 2 tag SNPs for genotyping.

Minor Essential Revisions:

1) Please add a comment about the genomic locations of the 3 genes you are studying.

2) In table 1, please provide specific p-values (such as with scientific notation) as opposed to 0.000.

Discretionary Revisions

1) The rs2069849 SNP in IL6 that was excluded due to low minor allele frequency was selected as a tag SNP and appears to have similar, if not increased, frequency as compared to HapMap CEU. It is a synonymous SNP. It
seems worthwhile to study.

**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.