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: Craig Hersh

Reviewer's report:

General comments:
The authors have performed a modest-sized case-control genetic association study, examining three genes for inflammatory markers, as well as the corresponding protein levels, as they associate to COPD risk and COPD phenotypes. They find an association between an IL6 haplotype and COPD risk. Interestingly, this haplotype is associated with lower CRP levels. Multiple other analyses are presented in the paper; this apparent lack of focus seems to detract from this association and some of the other interesting results.

Major compulsory revisions:

1. The most striking result from the biomarker analysis is that 40% of COPD patients did not have evidence of systemic inflammation. However, few additional details on this potentially important COPD subgroup are provided. For example, a comparison of clinical characteristics (as in Table 1) between the “inflammatory” and “non-inflammatory” COPD patients should be included.

2. If the non-inflammatory patients seem to represent a distinct COPD subgroup, based on clinical characteristics, then a genetic comparison between the “inflammatory” and “non-inflammatory” COPD patients would be justified.

3. In general, the SNP selection strategy and statistical analyses are appropriate. However, despite the authors' claim to the contrary, spurious association due to multiple testing is a concern, given the testing of 3 genes, 3 biomarkers, COPD risk, and 6 other COPD phenotypes (Table 8). Given this, the rationale for the Bonferroni p-value of 0.05/8 is not clearly explained. The haplotype-based analysis offers some protection against multiple testing, but replication in a second cohort would be ideal, especially for the association between IL6 and COPD risk. However, interesting results from the two revisions above might outweigh the limitation of the lack of a replication cohort.

4. Partly because of the multiple analyses, the paper seems a bit long, with too many tables. For example, Table 8 could be eliminated, as all results are non-significant. And Table 4 might be combined with Table S4, which both report the SNP-based analyses. If the focus is truly on the genetic results, then Tables 2 and 3 also seem excessive.

5. A recent paper reports association between IL6 SNPs and COPD risk (Cordoba-Lanus, Respiratory Medicine 2008). Please compare the current
results to this previous paper. This may help with the issue of replication in comment 3.

Minor essential revisions:
1. Table 1: I assume p-values listed as “0.000” mean p<0.001. Please correct.

Discretionary revisions:
1. Table 6: Including the p-values from score test and from logistic regression is confusing. Might be better to present one or the other.
2. Tables S1-S3 might be replaced by corresponding LD figures. This would help to limit the number of tables.

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

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.