Reviewer's report

Title: The role of IREB2 and transforming growth factor beta-1 genetic variants in COPD: a replication case-control study

Version: 1 Date: 5 October 2010

Reviewer: Yohan Bosse

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This is a nicely written manuscript studying the influence of polymorphisms in the TGFB1 and IREB2 genes on COPD susceptibility. There are a lot of controversies regarding the influence of TGFB1 on COPD susceptibility. Additional data are also needed to elucidate the 15q25 locus associated with COPD, lung cancer, and smoking behaviour. Accordingly the current study is valuable. The authors have interrogated the genes with SNPs significantly associated with COPD in previous studies. Briefly, they found SNPs in IREB2 associated with COPD risk.

In general, the study is well conducted and the genes studied are of great interest. It is a replication study, so there is only one population study, but well phenotyped and with adequate sample size. There is no functional work to validate the genetic association signal. Other concerns are addressed below.

Major Compulsory Revisions:

1) The authors should assess severity with lung function measurements and compared with the recent GWAS on lung function.

2) SNPs were selected based on previous literature. How well the genotyped SNPs cover the common genetic variants within these two genes? A comparison with HapMap SNPs would be appropriated.

3) A number of SNPs were tested in each gene, but there was no correction for multiple testing. The authors should adjust for multiple testing using a method that takes into account the level of LD, such as permutation or Nyholt (Am J Hum Genet 2004).

Minor Essential Revisions:

1) Table 3 should be replaced by LD plots.

2) The characteristics of all SNPs should be provided (call rate, HWE, location in gene).

3) Introduction (p. 5): “the expression of IREB2 has also been shown to be altered in lung tissue from COPD patients...”. A reference should be provided.

4) Does the inclusion criteria about smoking history of > 20 pack years also applies to control subjects? Table 1 seems to suggest differently. In the abstract,
the authors are referring to non-diseased smoking controls. Are they all current-smokers or ever-smokers?

5) Methods (p. 5-6): The first sentence of the second paragraph indicates that cases and controls were matched for ethnicity. This suggests that multiple ethnic groups were involved. However, in p. 6, we read that only Caucasians were recruited. This is confusing and should be adjusted.

6) Methods (p. 6): “To examine linkage disequilibrium, the correlation coefficient between SNP pairs...”. This should be replaced by “The linkage disequilibrium between SNP pairs...”.

7) Results (p. 7): Does any SNP failed HWE?

8) Results (p. 8), minor typo error: LD between rs2656069 and rs10851906 is 0.996 in the text, but 0.993 in Table 3.

9) Table 1: Considering the inclusion criteria, the mean FEV1/FVC ratio for control subjects seems low. Do they all have a ratio greater than 0.7?

Discretionary Revisions:

1) In the discussion, the authors mentioned that only one SNP is in relatively high LD with previous GWAS hits. Which GWAS studies were considered? Only COPD or others (i.e. lung function and lung cancer)? In addition, what is the size of the region that they have considered? Knowing the LD and the number of relevant genes in this region, the signal obtained with IREB2 might be caused by another more distant variant.

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.