Author's response to reviews

Title: Absence of association between SERPINE2 genetic polymorphisms and chronic obstructive pulmonary disease in Han Chinese: a case-control cohort study

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Author's response to reviews: see over
Dear Dr. Matthew Kaiser,

Thank you for giving us the opportunity to revise our manuscript. We have modified it according to the comments of the reviewer. In detail, we have addressed the issues as follows:

Referee 1:

Comment 1: The size of the study is modest with 327 COPD and 349 non-diseased smoking controls and could potentially miss weak effects e.g. odds ratios of 1 to 1.5 and some comment needs to be made about this since many genetic factors associated with identified to date tend to be in this range.

The power of our sample size with the OR range 1-1.5 has been calculated and the result was presented in page 10.

Comment 2: It is a little disappointing that the authors did not consider studying other SNPs within the SERPINE2 gene with minor allele frequencies of >5% as this would have provided further information about the gene in COPD. There are over 20 SNPs in SERPINE2 with minor allele frequencies >5%. It would be worth knowing in particular whether SNP rs 6734100 is associated with COPD as this was the most significant result obtained by Zhu et al (Amer Rev Respir Crit Care Med 2007). A comment needs to be made to reflect this. It would be unusual, for example, also to study 3 SNPs that are in complete linkage disequilibrium, though the authors chose them as they have been reported previously.
We added comments in discussion accordingly. The reason for genotyping all three SNPs instead of one tag SNP was to investigate whether they would yield different result as shown in DeMeo et al. 2006 AJHG. The detailed revision can be found in material and method (page 5-6) and discussion (page 10).

Comment 3: the comment about multiple testing is relevant, though the use of a Bonferroni correction may be too stringent and there is some debate over this in the literature. A comment should be included to reflect this.

We agree with the reviewer that Bonferroni is a little bit stringent for multiple testing. However, since other methods, such as false discovery rate, usually require all P value, which was not available in this case, we did not have other choice. We talked about this in page 11.

Comment 4: There are a number of better statistical packages available for data analysis though SPSS and PHASE is sufficient for the analysis undertaken. It would have posed some problems potentially if many SNPs were being investigated for example.

We revised the manuscript accordingly in page 8.
Comment 5: *some discussion about the quality control of the genotyping is warranted.*

*Although DNA sequencing was used and this is the gold standard for genotyping, the inclusion of known positive and negative controls in the assays used would have provided additional checks for the accuracy of genotyping.*

To guarantee the accuracy of genotyping, we determined these SNPs by bi-redirection sequencing. Moreover, some HapMap samples, whose genotype was known, were included in our resequencing as positive and negative controls. The revised details can be found in page 6.

In addition, the disease in title has been specified as “chronic obstructive pulmonary disease”. Our paper has be revised by two native English speakers and conformed to the journal style.

We hope you will find the revised manuscript acceptable for publication in *BMC Medical Genetics*.

Sincerely yours,

Ya-Ping Zhang