Reviewer's report

Title: Genetic influences on right ventricular systolic pressure (RVSP) in chronic obstructive pulmonary disease (COPD)

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Reviewer: Sally Chappell

Reviewer's report:

This paper reports the analysis of seven polymorphisms in six candidate genes in relation to right ventricular systolic pressure in COPD. The manuscript is generally well-written and presented logically, although the following comments need to be addressed.

Discretionary Revisions:

1. Background, 1st paragraph: It would be useful to clarify how many patients with COPD are affected by PH, rather than just saying “a significant number”.

2. Discussion, 4th paragraph: It would be useful to know further details about the conflicting study described in this section (reference 34). For example, a brief comment on the study size, ethnicity of subjects etc.

Major Compulsory Revisions:

1. My main concern with this manuscript is the significant number of statistical tests which have been carried out without any correction for multiple testing. I appreciate that the authors state they did not carry out these corrections due to the “exploratory nature” of the study (Discussion, final paragraph), but I feel that this is still something that should have been considered, even if by simply presenting both initial and corrected results. There also appears to be considerable multiple analysis done for the genotypes vs RVSP measurements, with ANOVA done initially, followed by two t-tests for each polymorphism (eg ACE II/ID vs DD as well as II vs ID/DD). Justification for this in the manuscript would be of benefit.

2. Table S3: Two comparisons are done for most of the polymorphisms (eg ACE II/ID vs DD as well as II vs ID/DD), but only one is done for the NOS3 VNTR (aa/ab vs bb). I would be grateful if the authors could confirm their reasons for this.

3. Background, 2nd paragraph: “Polymorphisms exist in vasodilator (nitric oxide synthase)…” This sentence indeed identifies that polymorphisms exist in the genes listed (which are the ones analysed in the current study), but polymorphisms also exist in the other genes which are referred to in the studies listed in the previous sentence of this section. For example, Reference 5 contains the analysis of a SNP in IL-6 in COPD-related PH. How and why did the authors...
chose the genes and polymorphisms included in the current study? Further information needs to be included regarding this.

4. Statistical methods, 2nd paragraph: It is good to see the authors consider power calculations in the manuscript. However, it would be useful to see this expanded in the Results or Discussion section, especially given the negative results observed for many of the polymorphisms that have been studied. If the negative results were associated with the lowest power for example, this would need to be commented on.

5. Genotyping: It would be useful to have brief details of the quality control measures in place for the genotyping assays, particularly given the deviation from Hardy-Weinberg equilibrium which is mentioned later in the manuscript (Point 7).

6. Results (Echocardiography), 1st paragraph: “Both these subgroups had similar characteristics to the whole cohort.” What about the significant difference seen for FEV1/VC ratio shown in Table 1 (p=0.026)?

7. Results (Genotypes) and Results (Association of genotypes with RVSP measurements): The NOS3-Glu298Asp SNP showed minor deviation from Hardy-Weinberg equilibrium in the total sample (p=0.02), and the EDN1 SNP shows some deviation in the RVSP group (p=0.04) though there is no comment about possible causes for this. I would like to see the authors comment on these results, particularly to reassure readers that this is not due to genotyping error.

8. Tables S3-S5: If mean differences between groups are being presented, the 95% confidence interval for these differences should also be included.

9. Discussion, 2nd paragraph: The authors propose that the NOS3 VNTR polymorphism may have a functional effect, but should also consider and discuss the possibility of other polymorphisms which are in linkage disequilibrium with the VNTR.

10. Conclusions: The association between ACE genotype and lower FEV1 is only significant in one of the t-tests (p=0.09 ANOVA, p=0.028 t-test II/ID vs DD, p=0.68 t-test II vs ID/DD), so I wonder how robust this association is. This locus is not one which reached significance in recent GWAS for lung function – perhaps the authors should acknowledge this in the manuscript.

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.