Reviewer's report

Title: Differences in serum SP-D levels between German and Japanese subjects are associated with SFTPD gene polymorphisms

Version: 2 Date: 17 November 2013

Reviewer: Branwen Hennig

Reviewer's report:

Thank you for carefully addressing all issues raised in the initial review. Most of the responses were satisfactory and in return changes to the manuscript were appropriate.

One main issue, however, remains in my view. The author state in the abstract “We conducted the present study to examine whether serum SP-A and/or SP-D levels in healthy subjects (HS) and patients with ILDs differ between populations with different genetic backgrounds.” This in my view would be addressed by initially testing the effect of SNPs on SP-D level in the different ethnic groups (as was done), testing the association between SP-D level and disease status in the different ethnic groups (as was done) and then testing whether SNPs affect case-control (i.e. disease) status adjusted for age, ethnicity and SP-D level in the multivariate analysis. Instead, the authors in the multivariate analysis tested for association between SNPs and SP-D level, adjusted for age, ethnicity and disease status. Yet in their response to point 3) the authors say that “It is beyond the focus of our study to test the correlation between ‘disease status’ and serum SP-D levels” – if disease status can be included as covariate, why not as outcome? Consequently, I am afraid, I still don’t follow the rationale behind the analysis undertaken.

Two other points caught my attention:

Given that the SNPs screened were largely selected due to known differences in genotype frequencies between Japanese and Caucasians, the results presented in the first section on page 12 table 3 are to be expected. Thus, this reflects a ‘confirmation’ rather than an entirely novel result and as such this section could be much abbreviated and moved e.g. to supplementary materials.

Finally, the much improved tables indicate that there seems to be a disparity in available genetic data. It is to be expected that genotyping may not be possible for all study participants for a variety of reasons (no DNA available, assay failed), but it seems missingness of genotype results is disproportionately large for German controls, with data available on only 37 out of 165 individuals. Could the authors outline why this is the case and whether this may have introduced any bias in the analyses (e.g. were those not genotyped different for baseline measurements to those genotyped?)?
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 I have no competing interests.