Author's response to reviews

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

Authors:

Yasushi Horimasu (yasushi17@hiroshima-u.ac.jp)
Noboru Hattori (nhattori@hiroshima-u.ac.jp)
Nobuhisa Ishikawa (nobuhi@hiroshima-u.ac.jp)
Sonosuke Tanaka (so_tanaka@saijoshimin-hosp.jp)
Francesco Bonella (Francesco.Bonella@ruhrlandklinik.uk-essen.de)
Shinichiro Ohshimo (ohshimos@hiroshima-u.ac.jp)
Josune Guzman (Josune.Guzman@ruhr-uni-bochum.de)
Ulrich Costabel (Ulrich.Costabel@ruhrlandklinik.uk-essen.de)
Nobuoki Kohno (nokohno@hiroshima-u.ac.jp)

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Author's response to reviews: see over
Differences in serum SP-D levels between German and Japanese subjects are associated with SFTPD gene polymorphisms

Dear Dr Giorgio Sirugo

Thank you very much for your reply. We would like to submit the revised manuscript that addresses the comments from the reviewer. We revised our manuscript using 'track changes' of MS Word and created additional files (Supplementary tables) as recommended by the reviewer. In addition, please find a detailed account of how each of the concerns of the reviewer has been addressed.

We greatly appreciate the opportunity to resubmit our work to BMC Medical Genetics and hope that it now meets approval for publication.

Sincerely, Yours,

Address correspondence to:
Noboru Hattori, MD, PhD.
Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8551, Japan.
E-mail address: nhattori@hirsohima-u.ac.jp
Telephone number: 81-82-257-5196
Fax number: 81-82-255-7360
Replies to the reviewers’ comments:

**The Reviewer 1: Dr. Branwen Hennig**

1) *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.*

Response:
We regret to say that the reviewer read too much into this sentence. It is beyond the focus of our study to test the association between “disease status” and SNPs in the SFTPD gene, and we believe that the readers will understand that this sentence does not necessarily mean to examine the influence of SNPs on disease status. Therefore, we did not revise this part of the abstract and hope that the reviewer would understand this point.

2) *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.*

Response:
In response to the reviewer’s suggestion, we deleted the description on Table 3 of the previous manuscript in this revision. Table 3 of the previous manuscript was also moved into the additional file as Table S2 in this revised manuscript.

3) *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?)?

Response:

We agree that the reviewer’s comment is reasonable. The genomic analysis could not be performed in a part of study participants, particularly in German HS, because collection of whole blood for DNA extraction was missed or refused. Following the reviewer’s suggestion, we compared subject characteristics including serum SP-A and SP-D levels based on the availability of genotype data in both the German and Japanese cohorts. As shown in Tables S1A and S1B of the additional files, no significant difference was found in serum SP-A or SP-D levels between the subjects with and without genotype data in HS and patients with IIPs of German or Japanese cohorts. We thus believe that the unavailability of genotype data in a part of study participants did not introduce significant bias in the results of this study. This point is also briefly described in the Results section of the revised manuscript (page 12).