Reviewer's report

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

Version: 1 Date: 1 October 2013

Reviewer: Digna R Velez Edwards

Reviewer's report:

Horimasu and colleagues evaluated SPD-D serum biomarker levels for association with interstitial lung disease as well as for corrections with SFTPD genetic variants, as well as for genetic differences between European and Japanese ancestry individuals. Although these findings are interesting I have a few concerns regarding the selection of genetic variants and the analytic approach.

Major Compulsory Revisions:
1. The motivation for selecting these specific four SFTPD genetic variants is unclear. According to the methods they were selected because of their genotype frequency differences between HapMap CEU subjects and JPT, rather than because of any specific prior association with disease. The authors then go on to highlight the finding that there were genotype frequency differences between German and Japanese subjects, is this really an unexpected finding given the SNPs were selected for having different distributions across these two populations? Why didn’t the authors select SFTPD variants that had been previously associated and then examine for ancestral differences?
2. The authors indicated that in their multivariate model they included ethnicity, do they mean they combined German and Japanese subjects or did they have another “ethnicity” covariate among German and among Japanese? If they did have ethnicity information among German and Japanese subjects then they should include that data in the demographic data table. If they combined German and Japanese subjects then the analyses are inappropriate and they should perform analyses stratified by German and Japanese subjects, particularly given that we know there are genotype frequency differences between these two populations for these SNPs.

Minor Essential Revisions:
3. Two of the SNPs (rs72917 and rs2243639) result in amino acid changes in the literature (missense) and one has previously associated with emphysema, interstitial pneumonia, and lung cancer (rs721917), an expanded discussion of the results in the context of this would be helpful.
4. The authors note in Table 1 that the healthy subjects differed for age and sex by the study populations (German and Japanese). Can the authors provide additional details regarding control selection across the two populations, were
there differences in the study protocol for controls across the two populations?

**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