Reviewer's report

Title: Folliculin mutations are not associated with severe COPD

Version: 1 Date: 8 August 2008

Reviewer: Laura Schmidt

Reviewer's report:

Folliculin mutations are causative of a rare inherited dermatologic disorder, Birt-Hogg-Dube' syndrome with associated lung cysts and spontaneous pneumothorax, and have also been found in the germline of patients with familial spontaneous pneumothorax. Chou et al. present a well defined study to assess the role of folliculin gene variants in the pathogenesis of generalized COPD. They analyzed 152 severe COPD probands for 7 folliculin mutations previously associated with FSP and BHD, and resequenced the folliculin gene in a subset of 41 probands. No patients were found to harbor any of the 7 mutations, and of the 31 variants identified in the resequencing effort, only 2 were predicted to have any functional effect. These two variants and two common non-coding polymorphisms were evaluated in an independent set of cases and controls with no association observed for any of the variants with presence of COPD or emphysema-related phenotypes.

The study is well designed using well characterized COPD subjects from a previously reported study, and adequate case and control sample sizes. Methods for sequencing and genotyping were appropriate and well described. Although nearly 30 folliculin mutations have been reported, the seven folliculin mutations chosen for testing were based on those reported in association with FSP and the common mononucleotide insertion/deletion mutation found in >50% of BHD patients and are, therefore, appropriate choices. The resequencing effort was extremely thorough, including all 14 exons, splice junctions, 5'UTR and 50 bases into intronic regions, and therefore, most likely detected all variants among the 41 probands. The careful re-examination of the two non-synonymous folliculin variants in an additional cohort of emphysema subjects and controls confirmed no association with COPD underscoring differences in molecular pathogenesis between FSP and early-onset COPD.

The limitations of the study were adequately discussed by the authors, including 1) the fact that rare variants may be limited to certain ethnic groups and these subjects were mainly Caucasian, 2) the fact that not all folliculin mutations identified to date were screened in this study, and 3) the severe COPD sample size was modest although similar to size of BHD cohorts reported.

Minor Essential Revisions:
1) Table S1 contains important data to support the conclusions of the paper and
should be included in the main manuscript not supplemental files.

2) Table 2 should include the literature reference for each of the mutations listed to document their discovery in previous work and enable the reader to evaluate genotype-phenotype associations.

3) Title of Table 2 should be corrected for capitalization, i.e., Boston and COPD.

4) Legend in Table 3 should state “Referenced to chromosome 17 “ not 7.

5) Figure 1 and 2 labels appear in the center of the figures not in the upper left or right corner and should be corrected.

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.