Reviewer's report

**Title:** Folliculin mutations are not associated with severe COPD

**Version:** 2  **Date:** 31 October 2008

**Reviewer:** Kuniaki Seyama

**Reviewer's report:**

I completely agree that this study is wonderful in terms of experimental methods and interpretation of the results they obtained. However, as far as the results were negative and they found that FLCN mutations were not associated with severe COPD, the point by which this study is decided to deserve to be accepted by J Med Genetics must be the rationale motivating scientists to initiate the study.

However, I, as a chest physician taking care of many patients with COPD and cystic lung diseases including BHD syndrome (BHDS), still do not find the strong rationale in this study even if other reviewers have given positive comments to this study. The only thing shared between COPD and BHDS seems to be emphysema. Emphysema can be recognized in COPD by both radiological examinations and pathology of the lungs, but cysts are usually the sole findings on radiological examinations in BHDS although emphysema can be sometimes recognized by pathological examinations of the lungs. Emphysema is not a pathologic finding specific for COPD, and likely to be found even in other lung diseases including interstitial lungs diseases, collagen vascular diseases and aged lungs. Clearly, emphysema is a minor finding in BHD.

I can not understand at all the idea that seven previously reported FLCN mutations identified in BHDS and FSP (this is likely to be BHDS limited to lung phenotype) were first genotyped in 152 severe COPD by the authors. Why do not authors think that some of 152 severe COPD should have shared the documented phenotype of BHDS? All seven FLCN mutations should be expected to cause similar clinical manifestations with BHDS since mutations were identified in patients with BHDS and the patients with the same racial background. Some of clinical manifestations of BHDS should be recognized even if severe COPD patients smoked a lot. I am surprised to know that the authors have paid no attention to phenotypic data of EOCOPD cohort.

I agreed with the authors’ claim that different mutations in the same gene may lead to different phenotypes. The rationale is here. Without genotyping seven know FLCN mutations identified in BHDS, the authors should have initiated bidirectional sequencing of all 14 exons and/or SNP typing of the genome encompassing the FLCN gene in a certain size of early-onset COPD cohort. In that case, I would have been able to find the rationale in this negative study.

**Level of interest:** An article of limited interest
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.