Reviewer’s report

Title: Folliculin mutations are not associated with severe COPD

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Reviewer: Kuniaki Seyama

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Major comments

This study described the results of mutation analysis of the BHD gene in patients with severe COPD. The methods the authors employed, the interpretation of the results they obtained, and the conclusion they made, look sophisticated and correct. However, the basic concept and the hypothesis which made the authors initiate to examine BHD mutations in COPD patients do not seem to make sense to me. A rationale with biological or scientific plausibility must exist between a target gene (the BHD gene) and a target disease (COPD) when mutation analysis of a single gene is performed in a disease.

Pulmonary manifestation of BHD mutation is the formation of cysts and not the development of emphysema. Radiologic appearance of cyst is totally different from that of emphysema and most of chest physicians and chest radiologists must be able to distinguish them easily. Accordingly, I can not understand the authors’ statements in conclusion (page 3) that FSP and COPD have distinct genetic causes, despite some overlap in radiographic characteristic. Recent studies revealed that BHD patients do not always have three phenotypic manifestations. In this context, FSP patients in whom BHD mutations were identified are no longer considered to be FSP, instead should be diagnosed as having BHD syndrome whose phenotypic expression was limited to the lung. The authors should understand this point and change description throughout the text. If the authors think of possible association of BHD mutations with early-onset severe COPD, the authors should collect the phenotypic data of Boston Early-Onset COPD (EOCOPD) patients. If the authors find that a certain fraction of patients in this cohort has fibrofolliculomas or renal tumors, then BHD mutation analysis will make sense in this cohort. In addition, the authors’ group has already published the results of genome-wide linkage analysis of this cohort several times and reported that chromosome 2q and 12p showed the strong association.

Taken together, this study lacks biological and scientific significance to analyze BHD mutation in EOCOPD patients

Minor comments.

1. What is the criteria to select 41 patients among EOCOPD patients for the entire BGHD gene analysis? This must be clarified.

2. Why 4 genotypes were selected to screen in NETT subjects and NAS subjects and to perform case-control analysis? This must be clarified. If authors would like
to find possible association between SNPs in and around the BHD gene and early-onset COPD, they should have genotypes all SNPs they found in NETT subjects and NAS subjects. The authors group has genotyped all SNPs of SERPIN2 gene and demonstrated their association with COPD. I strongly feel that this genotyping and association study is redundant.

3. In the legend for figure 1, there is a duplication of “indicates” on the last but one line.

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

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.