Reviewer's report

Title: RNAseq analysis of bronchial epithelial cells to identify COPD associated genes and SNPs

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Reviewer: Yao-Zhong Liu

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This is an RNA-seq study of bronchial epithelial cells (BEC) in COPD subjects vs. non-COPD controls. Targeted RNA-seq was performed on 35 genes in genome maintenance (GM) genes pathways. Through shrinkage linear discriminant analysis (SLDA), the authors identified 6 genes that discriminate COPD from non-COPD subjects with high CAT scores. The authors then proceeded to SNP-level analyses using dbGap GWAS databases and suggested that SNPs in the COPD classifier genes may contribute to COPD through cis-regulatory functions. Overall, this is a well performed study with sufficient details provided. I have a few comments as follows.

1. Can authors provide more details on analysis of differential allelic expression? For example, what statistical test was used and is there a p value associated with the test that supports statistical significance?

2. The authors may tone down cis-regulatory mechanism at SNP level in the discussion. The reason is that the gene with a SNP associated with COPD outcomes in GWAS datasets (which is ERCC5) achieved only a low CAT score of 0.06 in SLDA analysis.

3. Can authors provide rationale behind Figure 5? For example, what might suggest if we observe that allelic ratio at cDNA level is more variable than at gDNA level?

4. For the 6 genes that achieved high CAT score and discriminated COPD from non-COPD with good sensitivity/specificity (KEAP1, GPX1, CEBPG, XPA, CAT-2, and TP73-2), do they have cis-acting SNPs associated with COPD outcomes in the GWAS datasets?
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

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