Reviewer’s report

Title: Limited overlap in significant hits between genome-wide association studies on two airflow obstruction definitions in the same population

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Reviewer: John Holloway

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van der Plaat et al. address an important question in the genetic study of COPD, namely lack of overlap between different genome wide association (GWAS) studies of airflow obstruction. While there may be many causes of lack of replication between studies (e.g. differing ethnicity of study populations, differing GWAS platforms / imputation methods etc.), one significant factor is likely to be phenotype definition. Specifically, with regard to airflow obstruction, the differences in case definition between FEV1/FVC ≤ 0.7 and LLN methods. To address van der Plaat et al. present the analysis of both phenotypes in non-smoking and ever smoking subjects in the Lifelines cohort with replication in two independent cohorts.

No Bonferroni significant associations (p<2.19x10^-7) were found with either ratio or LLN measures of obstruction in either cohort. Interestingly, when relaxing the p-value to 10^-4 the overlap in identified SNPs was only 3% and 6% (never smoker and smokers respectively) between the definitions of airway obstruction (~30 SNPs above the 10^-4 threshold for each of the 4 conditions/definition groups).

This is an interesting observation and if the authors interpretation is true, that the two definitions of airway obstruction are measuring different phenotypes with different genetics risk factors is of importance to the field. However, I have some concerns.

Key comments:

Given the sample size of both discovery and replication cohorts and the fact no SNPs were significant at boneferroni corrected significance levels, do the authors feel that the lack of overlap between phenotype definition just represents the fact that very few real associations are represented in the list of SNPs that are being compared between the two phenotype definitions - there is only approximately 30 SNPs crossing even the 10^-4 threshold and the lack of overlap might simply reflect that most of these are occurring by chance due to the relatively small size of the cohort? In some ways to better address this point would be to undertake retrospective analysis of GWAS data in a large adequately powered study using the two phenotype definitions.

With regards to the two overlapping signals in the never smokers, FABP7 and NFYC(-AS1). Have the authors considered looking up these SNPs in a large GWAS for lung function / COPD (e.g Wain LV et a. Nature Genetics 2017;49:416-425)? If so, is there evidence of association with FEV2, FVC or ratio?
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?
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No

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