Reviewer's report

Title: Association of genetic variants in chromosome 17q21 with adult onset asthma in a Chinese Han population

Version: 1 Date: 6 August 2011

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Qiu and colleagues studied the genetic associations between adult-onset asthma and five single-nucleotide polymorphisms (SNPs) on 17q21 locus in 710 Chinese Han cases and 656 controls. They found all SNPs to be associated with asthma diagnosis, and three of them correlated with the expressions of ORMDL3 and GSDMB in leukocytes.

Since the first publication in 2007, chromosome 17q21 locus has been widely replicated in many ethnic groups including southern Chinese in Hong Kong. However, most studies including the recent GWAS meta-analysis found this locus to be linked mainly to childhood-onset asthma. This manuscript is thus important to support that the association between asthma and 17q21 also applies to adults. The study design is straightforward and genotyping is adequately described and performed. However, the authors need to address a number of issues to improve this manuscript.

Major Compulsory Revisions

1. Statistical analysis

The authors reported in Table 3 single-marker associations between asthma and five SNPs. Such analyses were not adequate to clarify the genetic associations, and the authors need to confirm the results by adjusting for important covariates such as age and sex using multivariate regression. It would also be interesting to know whether 17q21 locus is linked to spirometric parameters. Besides, the results should be adjusted for multiple statistical comparisons. In addition, the authors need to analyze the association between asthma and haplotypes based on the five studied SNPs.

2. Clinical phenotypes

Most published studies reported 17q21 locus to be important for the susceptibility of childhood-onset asthma. A substantial number of children with asthma continue to suffer from this disease as adults, but some adults may report uncertain or even inaccurate recall as to the onset of their disease (especially the milder cases). The authors need to acknowledge this issue as a limitation. The other major issue relates to the source from which controls were recruited. Were they healthy volunteers from the community, or attendants of the hospital who did not have asthma history? I am concerned about their lung function (Table 1), with low FEV1 and/or FVC in a subgroup of these controls. Lastly, how did the
authors select the 61 cases for studying gene expressions? Were they consecutive patients seen in their clinics or only a biased group of subjects who consented for this additional testing?

Minor Essential Revisions

1. SNP selection
The authors chose five SNPs that were reported to be significant in published studies. Were these SNPs also tagging for 17q21 locus in the Chinese Han population? If not, why did the authors not include the more important tagging SNPs in their population? Were the five SNPs studied in linkage disequilibrium with other SNPs on this locus.

2. References
The citations for several references are incomplete (e.g. #2, #5, #18 and #20). The authors also need to cite the GWAS meta-analysis recently published by the GABRIEL Consortium (Moffatt MF et al. N Engl J Med 2010;363:1211-21), and discuss the findings of this manuscript in the context of that landmark GWAS.

Level of interest: An article of importance in its field

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.