Reviewer’s report

Title: Association analysis of ILVBL gene polymorphisms with aspirin-exacerbated respiratory disease in asthma

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Reviewer: Ian Sayers

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This is an interesting study looking at the potential contribution of nine genetic polymorphisms within the ilvB acetolactate synthase like (ILVBL) gene and risk of aspirin-exacerbated respiratory disease (AERD) using a 141 AERD and 995 aspirin-tolerant asthmatic (ATA) subjects. Overall, there was some modest evidence of association between several single nucleotide polymorphisms and risk of AERD, however these variants did not show association with decline in FEV1 in the aspirin challenge test. ilvB acetolactate synthase like (ILVBL) is involved in branched-chain amino acid biosynthesis and it remains unclear regarding the potential role of this gene in AERD.

While of interest several issues need to be resolved prior to potential publication:

Main comments

1. It is unclear how the current study is different from these data presented in the Authors published work which highlighted the association of ILVBL gene polymorphisms with AERD as part of a GWAS (PMID: 23180272). This needs to be clearly stated including the difference/overlap in the patients used for the current and previous work.

2. In the demographics table, it is interesting that the AERD subjects have greater BHR (meth), is this related to response to ASA in the challenge?

3. The study would benefit from power calculations for each analyses to put these data in context, please include.

4. Many significant p-values are based on very few patients per group, >10. This needs to be clearly discussed and a more realistic threshold for minimum groups size used throughout.

5. The lack of a replication component to the study and potentially a meta-analyses to more accurately assess effect sizes is a major limitation, can this be provided?

6. There seems to be a large number of tests, e.g. two outcomes, nine SNPs using 3 genetic models therefore it would be useful to include a discussion of multiple testing in light of the findings.
7. There needs to be more discussion of the association signals/potential causative genes including an eQTL based analyses to identify the most likely mechanisms, e.g. rs2240299 included in the study is in high linkage disequilibrium with a missense mutation in SYDE1. Please include an eQTL analyses (e.g. via ENCODE) and more discussion.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**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.

No

**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

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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