Reviewer's report

Title: Genome-Wide Methylation Profiling of the Bronchial Mucosa of Asthmatics: Relationship to Atopy

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Reviewer: Agustin F Fernandez

Reviewer's report:

In this manuscript Kim YJ et al. describe a specific pattern or signature of DNA methylation that discriminates between atopic and non-atopic asthmatics. The experimental design is clear and the manuscript is well-written. Illumina methylation arrays is a robust and powerful tool to measure DNA methylation levels of many genes, but the interpretation of results must be done carefully.

Major Concerns

- The key weakness in this paper lies in the small methylation differences (in Beta values) found between different groups. Beta value differences between 0.1-0.14 (Table 2, 3) are at the limit of sensitivity of the array. Biological validations (10-15 new samples) using bisulfite pyrosequencing should be performed for candidate genes (differentially methylated) in order to clarify this issue.

- The array data analysis should be described in more detail in order to avoid confounding factors, for instance, it is crucial to clarify if the samples were hybridized in the same array (chip-slide). If not, was the batch effect among arrays corrected? Are probes with high detection p-values avoided in the analysis? It was stated (in results) that methylation of X-chromosome was not considered in the analysis, but in Table 3 some of the candidate genes are located in X chromosome. Please, explain this issue.

Minor Concerns

- In the section of Background (page 5) Epigenetics is defined but it is called "Epigenesis".

- In the section of Methods, the terms NC and BA appeared but they are not defined anywhere in the text.

- Explain what is represented in figure 2A-1 and 2B-1: comparison of individual samples or average values per group.

- Figure 2C is confusing. In the text, (Results, page 6) it is stated that the heatmap represents 55 CpG sites, but in the figure legend it is indicated that 2904 methylated CpGs on chromosome1 are shown.

- The terms hypomethylated and hypermethylated are used at the end of the Results. They should be defined previously to clarify exactly what they refer to.

- This sentence in Discussion should be deleted or changed: "These data
indicate that the global gene expression patterns of BA and NC are not different, at least based on the samples studied". Associations between DNA methylation and expression have not been tested in this work. If the authors prefer to keep the sentence, they should indicate that their data suggest…

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**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