Reviewer's report

Title: Whole-exome sequencing of a pedigree segregating asthma

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Reviewer: Iuliana Ionita-Laza

Reviewer's report:

The authors discuss a study on exome-sequencing of a family with multiple asthmatic children. Within this family, the authors used a filter-type methodology to identify rare, non-synonymous variants which are not in public databases and which segregate with asthma. They identify ten such variants, and discuss in more detail three genes that are particularly interesting based on functional information of variants in these genes and existing information on their association with asthma. They also show that affected children are enriched in novel, non-synonymous variants in 251 asthma candidate genes compared with their unaffected siblings.

The article is well written, with analyses clearly presented. A weakness of the paper is that there is no formal statistical testing, and this makes it difficult to judge the statistical significance of the results. The paper certainly merits publication, with the caveat that the results are only hypotheses that need to be tested within a more rigorous framework.

Several other comments:

Major Compulsory Revisions

The number of de-novo variants identified per individual seems quite high, much higher than the expected number per individual. I suspect many of those are not real, a point that the authors acknowledge as well. What is the ratio of transmitted to untransmitted variants overall? I suggest the authors use very stringent criteria to identify the de-novo variants.

For the analysis on the enrichment in novel, non-synonymous variants for affected children compared to their unaffected siblings, can the authors perform an exact test to assess the statistical significance? That would be more convincing.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

No