Reviewer's report:

Title: Genetic analysis of an allergic rhinitis cohort reveals an intercellular epistasis between FAM134B and CD39

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Reviewer: Aurélie Cobat

The manuscript entitled “Genetic analysis of an allergic rhinitis cohort reveals an intercellular epistasis between FAM134B and CD39” by Rossella Melchiotti et al. reports a genetic interaction between a CD39 promoter variant (rs7071836) and a variant upstream the FAM134B gene (rs257174) in the control of allergic rhinitis (AR). The authors show that both variants are cell specific eQTL for their respective gene. Further functional studies negatively correlate expression of CD39 and FAM134B in whole blood. Finally, the authors suggest that CD39 Treg expression affects FAM134B monocyte expression through extracellular ATP levels.

The key finding of the study is the identification of a genetic interaction in the control of AR. However, I have a major comment regarding this finding:

1/ Using a cut-off of 10^-4, 58 candidate interactions with the CD39 promoter variant rs7071836 were identified and 20 were selected for replication. Selection of the 20 SNPs and threshold used to claim replication should be described. Indeed, 20 variants selected sounds like the limit to have a replicated signal after correction for multiple testing (assuming that p-value reported are for a bilateral test and that replication is judged on unilateral p-values).

In addition, I have minor comments:

2/ In the epistatic interaction section, I guess the p-value and OR stand for the interaction term? This should be explicitly noted. In addition, I’d like to see, at least in the Table, marginal ORs and p-values for the 2 SNPs.

3/ If possible, a plot of FAM134B expression level according to rs7071836* rs257174 genotype could benefit the reader to better understand the interaction.

4/ The authors have linked CD39 and FAM134B by extracellular ATP levels. What is the hypothesis regarding the link with RA?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests