Author's response to reviews

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

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Author's response to reviews:

Dear Editor-in-Chief,

Please find enclosed our manuscript by Melchiotti et al. “Genetic analysis of an allergic rhinitis cohort reveals an intercellular epistasis between FAM134B and CD39” for consideration for publication in BMC Medical Genomics.

In this manuscript we describe for the first time an intercellular epistasis. We validate the finding in a number of replicate cohorts, and also show some mechanistic interaction between the epistatic partners. Specifically, a polymorphism modulating the expression of CD39 on Treg cells is genetically and functionally linked to a SNP controlling FAM134B expression in monocytes, and is associated with allergic rhinitis (AR).

CD39 is an important ecto-enzyme involved in immune regulation. We have previously shown that CD39 expressing regulatory T cells (Treg) can catalyze the hydrolysis of extracellular ATP and ADP to AMP. Polymorphisms associated with CD39 have been linked to a number of immune disorders (e.g. Crohn’s disease, Friedman et al., PNAS, 106:16788-93, 2009). However, CD39 has never been directly linked to AR.

FAM134B is a cis-Golgi protein previously shown to be associated with severe sensory and autonomic neuropathy. It has not previously been shown to have any immune system involvement.
We have further shown in the manuscript that together the polymorphisms affect susceptibility to allergic rhinitis in a synergistic way, and that the epistasis appears to be driven by extracellular ATP, previously reported to be the substrate of CD39 and as shown by us in this manuscript an inducer of FAM134B expression.

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript and agree with its submission to this journal.

Sincerely,

Michael Poidinger