Author's response to reviews

Title: Evaluation of the toll-like receptor 6 Ser249Pro polymorphism in patients with asthma, atopic dermatitis and chronic obstructive pulmonary disease

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Author's response to reviews: see over
Reviewer #1

“I believe that the authors have addressed all of the criticisms raised by the reviewers and that the manuscript is much improved. I do think that it would be worthwhile including a comment in the middle paragraph on Page 7 suggesting that the results may be due to linkage disequilibrium, not to the specific functional variation. The authors are hinting at this but they don’t say so directly.”

We mention on page 7, bottom paragraph, that the Ser249Pro polymorphism might not be disease-causing by itself, but instead be in linkage disequilibrium with the true disease-causing variation.

“I also believe that the arguments provided by the authors that suggest that adult controls are appropriate for adult asthma are specious, while phenotyped children with similar observation time would be the most appropriate control group. Adult, non-asthmatics may be different from childhood non-asthmatics and may simply not be the most appropriate control group, but there is nothing that can be done about this particularly, and I think that the authors have done a good job in answering all of the other criticisms noted by all three reviewers in the previous review. I would now say that this paper is acceptable for publication.”
Reviewer #2

“The authors submit a revised version of a manuscript that studies the association between the Ser249Pro SNP in TLR6 and asthma, COPD, and atopic dermatitis. The major flaw that I had pointed out in the first version was that the control group of non-asthmatic adults was not an appropriate control group to be compared with the cases of childhood asthmatics, which was the only statistically significant finding. The authors respond that they specifically chose adults for the control group because "the risk remains very high for asymptomatic children to develop an allergic disease during childhood or even adulthood." Thus, they argue that a control group composed of children would only be valid if they were "followed to adulthood to verify that they do not develop an allergic disease later on." However, this logic should also be applied to the pediatric asthma cases. The natural history of asthma is complex, but involves remission of disease. In one of the articles that the authors cite (reference # 24, De Marco et al), the overall remission rate for childhood asthma was found to be 45.8%. Thus, they would need to follow the pediatric cases to adulthood to make sure that their asthma does not remit. Alternatively, some of the adult controls may have had "asthma" as a child, but not as an adult. Either way, I do not feel that the authors make a convincing enough case to reverse my original opinion that the controls are not appropriate for the childhood asthma cases.”

The asthmatic children included in this study are being followed-up regularly in the Pediatric Pneumology Study Center in Bochum to make sure that they really have childhood asthma and do not fall in the category of children with transient wheezing that is lost after 3 years of age. Furthermore, even though the remission rate of childhood asthma is quite high, we investigated the phenotype "childhood asthma" and not "asthma persisting from childhood into adulthood".

The adults we chose as controls were asked specifically whether they had any signs of allergic symptoms or asthma during their lives and were only included if they answered this question in the negative.

Therefore – in respectful disagreement with reviewer 2 - we still believe that the control group is valid for the analysis.
Reviewer #3

Minor essential revisions:

1) “In tables 2 and 3, C should be changed to Pro and T should be changed to Ser to avoid confusions.”

We have made the changes in tables 2 and 3 (pages 18 and 19).

Discretionary revisions (which the author can chose to ignore):

2) “The authors interpreted their results as a weak association of the 249Ser allele with childhood asthma. Also, an opposite allele was associated with childhood asthma as compared with the one reported by Tantisira et al. Because the authors did not replicate the initial findings of Tantisira et al., the corrected $p$ values should be applied to their study. I would interpret this study as a negative association, with a trend that 249Ser allele was more observed in pediatric asthmatics than in controls.

You may be quite right.