Author's response to reviews

Title: Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms: New data and a meta-analysis.

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Version: 3
Date: 20 October 2014

Author's response to reviews: see over
MS: 2983673913351277

Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms: New data and a meta-analysis.

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BMC Gastroenterology

Dear Editor,

We appreciate the time and effort spent by you and the referees in reviewing our manuscript and for your helpful comments. Attached, please find a revised form of our manuscript, in which we have addressed the concerns raised by the editorial board. The changes were applied and highlighted in the revised manuscript.

We hope that our revised and improved manuscript will be acceptable for publication in BMC Gastroenterology.

Thank you for your consideration.

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We would like to inform you that almost all the required modifications were accomplished except for the last one:

1. In the sentence "Two single nucleotide variations, corresponding to two amino acid polymorphisms for TLR4, were analyzed: the Asp299Gly (896A/G), rs4986790 and the Thr399Ile (1196C/T), rs4986791 mutations." please take out the word "mutations".
   Done

2. In sentences such as "studies without the raw data of the TLR4 Asp299Gly, Thr399Ile genotypes" please replace "," with "and" (so it would become: "studies without the raw data of the TLR4 Asp299Gly and Thr399Ile genotypes.
   Done

3. Abstract: "The study population comprised 117 patients with IBD and 112 healthy unrelated blood donors"; results: "Hundred and fourteen patients with IBD (83 CD; 34 UC) and 112 control subjects from the general population were genotyped for the presence of TLR4 Asp299Gly and Thr399Ile polymorphisms" - please match the numbers (117 vs 114)
   Done

4. "Nevertheless, in patients with UC, genotype and allele frequencies distributions for Asp299Gly polymorphism (X2 = 0.03, P = 0.86) were in Hardy-Weinberg equilibrium but not for Th399Ileu polymorphism (X2 = 19.05, P <0.001)." the word "nevertheless" should be omitted from this sentence.
   Done

5. "No significant difference was noticed in Allele distributions of the Asp299Gly polymorphism between the control and patient groups." change Allele to allele.
   Done

6. "However, meta-analysis demonstrated significantly higher 299Gly and 399Ileu frequencies in IBD, yet for subgroup analysis, no significant association is reported for 299Gly carriage in UC patients. This sentence is unclear, why would you report no significant association in UC? Please rephrase to say that association was observed to IBD and CD for both SNPs and to UC for one (if it is correct).
   Done

The new results section on meta analysis is unclear, in particular:

7. The results section should contain the number of cases and controls included to meta-analysis. Done
8. This sentence should be reformatted: "The overall OR was (OR = 1.35, 95% CI: 1.12-1.38; P = 0.0001) (figure 1)."

Done

9. In the other hand, UC patients presented 359/5184 risk alleles, while 457/7244 G alleles were found in controls (table 2). These numbers are not useful for the readers, please use % and add a conclusion? what message do you give by this sentence?

The required modifications were done

10. In the present meta-analysis, a lack of heterogeneity between studies was observed for? Please rephrase for? we did not observed heterogeneity between studies for?

Done

11. Please be consistent with using names of the SNPs - Th399ILeu is a typo, either T399I or Thr399Ile should be used consistently. Same about the other SNP (once named as D299G).

Done

12. Given the evidence that an altered innate immune response and chronic inflammation are implicated in IBD pathogenesis, genetic influence of PRRs was clearly suggested? put PRR in words.

Done

13. Don?t put every sentence as a new paragraph in discussion.

Done

14. Please add power calculations and acknowledge in the discussion the low power that you have to identify association in your population.

Done

15. Please add sample size (number of cases and controls) to the tables.

Done

16. Table 4 contains formatting mistakes (?mars-90?)

Corrected

17. Please add p-values to the tables.

Done

18. Please add correction for multiple testing in sub-phenotype analysis and indicate if any of the associations were significant after correction for multiple testing.

We believe that correction should not be applied since each sub-phenotype test was considered separately as independent analysis.