Author’s response to reviews

Title: TNF-α−308 G/A and IFN-γ+874 A/T gene polymorphisms in Saudi patients with cutaneous leishmaniasis

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Dr. Kamlesh Guleria /Dr. Matteo Pasini
Editors,
BMC Medical Genetics

Dear Dr. Guleria/Pasini:

Thank you for giving us the opportunity to revise our manuscript MGTC-D-19-00560, entitled “TNF-α−308 G/A and IFN-γ+874 A/T gene polymorphisms in Saudi patients with cutaneous leishmaniasis”. The manuscript has been revised in light of the reviewer’s comments for publication in BMC Medical Genetics. The material contained in the manuscript is original and has not been submitted for publication elsewhere.
We have addressed all the concerns raised by reviewers as detailed under the enclosed point-by-point reply to the reviewers.

We continue to express our gratitude to the reviewer’s constructive criticisms, which have improved the quality of the manuscript. We hope that the reviewers will find the answers satisfactory.

Sincerely,

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POINT-BY-POINT REPLY TO THE REVIEWERS’ COMMENTS

Manuscript Reference: MGTC-D-19-00560
Manuscript Title: TNF-α−308 G/A and IFN-γ+874 A/T gene polymorphisms in Saudi patients with cutaneous leishmaniasis
Journal: BMC Medical Genetics

We are grateful to the reviewers for thorough review and for their constructive comments, which enabled us to further improve our manuscript. Concerns raised have been addressed below. Please note that all the changes in the revised manuscript are highlighted.

Reviewers Report:

Bhavi Modi, Ph.D. (Reviewer 2):

The manuscript by Ahmed AA et al describes the results of a case-control study testing association between individual polymorphisms in the TNF-α and IFN-γ genes and the susceptibility to infection by different Leishmania species among Cutaneous Leishmaniasis patients in central region of Saudi Arabia. While the study findings are of great interest, several important key issues require clarification and consideration. The manuscript in its current state lacks significant details in outlining the background and known literature surrounding the host susceptibility to Leishmania infections, etiology and health impact of CLs, role of immunologic factors and more importantly genetic factors (genotype differences) in disease pathology. Adding this will further help to define the rationale and study objectives in a better fashion to fully appreciate the significance of the study findings. In addition, several grammatical errors & issues with sentence framing and structure need to be fixed as these are impeding proper understanding of the manuscript and make digesting the information provided difficult.

Author’s Response:
We highly appreciate for your thorough review and for the positive comments. The manuscript has been revised in lights of your suggestions.
Specific comments and questions that need addressing:

Comment 1:
Background: Specific questions that need addressing in this section are: What are the different factors that influence different outcomes of Leishmania infections? What is Cutaneous Leishmaniasis and what is the disease etiology? Are specific Leishmania species more commonly associated with CL in certain geographical areas? Are variances in outcomes mostly related to environmental factors such as temperature, host nutrition status, specific species, co-infection with other pathogens or do genetic factors influencing host immune response and therefore creating a 'genetic susceptibility' model play a major role as well? While the authors may have loosely tried address some of these questions (the prose makes it difficult to follow), a more in-depth review of existing literature addressing these questions should be included to demonstrate the progression to current study objectives.

Author’s Response:
We highly appreciate for your thorough review and pointing these out. As suggested, background section has now been revised. The factors that influence the onset of leishmania infections have now been included. We have also described the cutaneous leishmaniasis and its associated etiological factors in the background of the revised manuscript. The geographical areas commonly associated with the L. species have also been added. Not only have these, we environmental factor such as temperature, humidity or desert regions associated with the infection have also been described in the background of the revised manuscript. Please see the highlighted additions in the background on page 3, line 6-20 and page 4, line 1-5 of the revised manuscript. Please note, all changes in the revised manuscript are highlighted.

Comment # 2.
The two specific variants under study should be identified by their 'rs' identifiers and with standard HGVS nomenclature so readers can easily evaluate specific criteria associated with the variant that they might be interested in. Other information about their population prevalence/allelic frequency (from databases like gnomad), predicted or known functional impact and relevance should be reported. This will not allow for comparison (of allelic frequencies etc) of controls used in the study with the general population but will also help understand study objectives and findings in a more meaningful context.

Author’s Response:
Thanks for your excellent suggestions. As suggested, the ‘rs’ identifiers of the variants have now been included in the methods section on page 6, line 8 and also in table 2 of the revised manuscript. We highly appreciate for your suggestion on the population prevalence/allelic frequency, but our searched from the database didn’t find suitable information to report.

Comment # 3.
Methods: What were the exclusion criteria (if any) established for selection of the control subjects in the study? For e.g. were they screened for presence/absence of infections (Leishmania and/or other pathogens?) before inclusion in the study?. In addition, how were the cases/CL patients identified? What were the diagnostic criteria used? Were any immunologic criteria used
to inform selection in the study? Reporting the specific inclusion and exclusion criteria for all study subjects is a requirement of a well designed case-control study and the authors fail to provide this information.

Author’s Response:
Thanks for your excellent review. The inclusion and exclusion criteria for the selection of the L. cases and normal human controls have now been included in the methods section of the revised manuscript on page 5, line 12-21.

Comment # 4.
Results: Tables 3 and 4 outline the key results of the study and are very interesting findings. Another study question that could add value to this section is testing the association of both minor alleles combined (i.e. presence of both TNF-α A allele and IFN-γ T allele in an individual) and infection susceptibility in cases compared to controls. Does having both minor alleles increase/ decrease susceptibility to Leishmania infection in general or to individual L. species? This might provide additional insights into genetic mechanisms of host immune response as these factors work together in a pathway and not in isolation.

Author’s Response:
Thanks for your thorough review and the excellent suggestion; this definitely helped us to further improve the quality of the manuscript. As suggested, the data on synergistically combined TNF-α 308 and INF-γ 874 alleles with the susceptibility of L. infection have been included in the abstract on page 2, line 14-16, line 22; page 3, line 1&2; in results section on page 8, line 17-23; page 9, line 1-4 and discussed in the discussion section on page 11, line 8-14, 20-22 and also in the last part of the conclusion section on page 12. The complete details of the synergistically combined genotype frequencies of TNF-α-308 and INF-γ 874 have been given in the newly added Table 5.

We believe that the revised manuscript will now meet the high standards of the journal and suitable for “BMC Medical Genetics”.

Dr. Zafar Rasheed
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