Author’s response to reviews

Title: Association of matrix metalloprotease 1, 3, and 12 polymorphisms with rheumatic heart disease in a Chinese Han population

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Author’s response to reviews:

Dear Matteo Pasini,

We greatly appreciate the efficient, professional processing of our paper by your team.

We tried our best to revise the manuscript and made some changes in the manuscript according to the reviewer’s comments. These changes will not influence the content and framework of the paper. And here we listed the changes in “Appendix” below and marked with "Revision" Tool of Microsoft Word in revised paper. The main corrections in the paper and the responds to the reviewer’s comments are as flowing.

Once again, Thanks very much for your kind work and hope that the correction will meet with approval.
With kindest regards,

Yours Sincerely

Zhaohui Meng

Replies to Reviewer 2:

Dear Prof. Angelica Beate Winter Boldt,

Thanks you very much for your constructive comments and suggestions.

Those comments are very helpful for improving our paper. We have studied comments carefully and have revised the manuscript according to the comments and suggestions. The main corrections in the paper and the responds are as flowing, and here we listed the changes in “Appendix” below and marked with "Revision" Tool of Microsoft Word in revised paper. We hope this revision will meet with your approval.

Once again, thank you very much for your hard work.

With kindest regards,

Yours Sincerely

Zhaohui Meng

Comments and Reply

1. The answers to the first questions "Why it is important..." and "Why only..." are good and should be summarized and incorporated in the abstract itself. For example, instead of "It has been suggested that genetic susceptibility play an important role in the development of rheumatic heart disease (RHD).", write a sentence with the answers to the questions (you answered only to me, but this will help the reader to understand, at first glance, the importance of your work). Do also include the missing information in the introduction, as well as the references cited here.

Answer: Thank you very much for the good suggestion. We have rewritten the background in abstract to make it more informative, and the missing information was included in the introduction, as well as the references cited here.

2. With FDR, I meant Benjamini-Hochberg correction, but the p values with the new statistical analysis are acceptable.
Answer: Thank you for your valuable suggestions and approval regarding our statistical analyses.

3. Please rephrase "Therefore, different ethnic groups and diseases may lead to diversity in polymorphism research."

Answer: We have rephrased the sentence in the discussion according to your suggestion.

4. Please include your inability to provide functional results, as one of the drawbacks of your work, in the conclusion. Nevertheless – adequately cryopreserved RNA and serum samples can well be used after one year – maybe you don't have them?

Answer: We have added additional remarks about the absence of functional results in the discussion and conclusion.

In the present study, we mainly focused on MMPs polymorphisms and most of the serum samples in this research were cryopreserved. In our future study, RT-PCR or other experimental methods will be used to illustrate our results.

Thank you again for your constructive suggestions.

appendix

1. Abstract Part:

Line 17-20, “It has been suggested that genetic susceptibility play an important role in the development of rheumatic heart disease (RHD). The purpose of this study was to evaluate the association of matrix metalloprotease 1, 3, and 12 (MMP1, 3, and 12) polymorphisms with RHD in a Han population in Southern China.” was deleted.

Line 20-25, “Rheumatic heart disease (RHD) is an autoimmune disease triggered by acute rheumatic fever (ARF). Matrix metalloproteinases (MMPs) play an important role in the modulation of immune responses. The purpose of this study was to evaluate the association of MMP1, 3, and 12 promoter polymorphisms with RHD in a Han population in Southern China since the 3 genes are localized on the same chromosome and have a combined effect.” was added.

2. Background Part:

Line 54-60, “Twin studies have found that the risk of ARF in monozygotic twins with a history of ARF is increased by more than 6 times compared to that of dizygotic twins [10]. These findings provide evidence for the involvement of a host of genetic factors in susceptibility to RHD, which is the sequel to ARF in endemic conditions. Genetic association studies have shown that methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with RHD [11] and other studies have suggested genetic associations between promoter
polymorphisms in angiotensin-converting enzyme (ACE) and interleukin 10 (IL-10) and RHD [12, 13].

" was deleted.

Line 61-73, “Matrix metalloproteinases (MMPs), which are members of the multidomain zinc endopeptidases family, are not only capable of degrading many ECM components associated with valvular remodeling and calcification [10], but they also can modulate immune responses by processing cytokines and chemokines to change their activity [11]. McQuibban GA et al [12] demonstrated that the N-terminus of monocyte chemoattractant protein 1 (MCP1), MCP2 and MCP4 was cleaved by MMP1 and 3 to produce antagonist factors which dampen inflammatory processes. Further study has shown that MMP3 has a dual role in biphasic modulation of inflammatory mediator activity by cleaving Interleukin 1β precursor into active form and degrading the biologically active cytokine [13]. We can speculate that MMPs may be involved in the pathogenesis of RHD through an immune mechanism. However, there are few reports on the relationship between MMPs and RHD. In the present study, we will investigate the effect of MMPs polymorphisms on RHD.” was added.

Line 74-76, “Matrix metalloproteinases (MMPs), which are members of the multidomain zinc endopeptidases family, are capable of degrading many ECM components associated with valvular remodeling and calcification [14].” was deleted.

3. Discussion part:

Line 170-176, “Twin studies have found that the risk of ARF in monozygotic twins with a history of ARF is increased by more than 6 times compared to that of dizygotic twins [31]. These findings provide evidence for the involvement of a host of genetic factors in susceptibility to RHD, which is the sequel to ARF in endemic conditions. Genetic association studies have shown that methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with RHD [32] and other studies have suggested genetic associations between promoter polymorphisms in angiotensin-converting enzyme (ACE) and interleukin 10 (IL-10) and RHD [33, 34].” was added.

" was added.

Line 225-226, “Therefore, different ethnic groups and diseases may lead to diversity in polymorphism research.” was deleted.

Line 226-227, “The cause of the different conclusions may be difference in study population, low sample size or poor control-patient matching.” was added.

Line 243-244, “Fourth, we did not use different methods to validate our results, such as RT-PCR, ELISA and/or immunohistochemical analysis.” was added.

Line 185, “[31, 32]” was corrected as “[35, 36]”. 
Line 188, “[8, 33]” was corrected as “[8, 37]”.

Line 190, “[34]” was corrected as “[38]”.

Line 196, “[35]” was corrected as “[39]”.

Line 203, “[36, 37]” was corrected as “[40, 41]”.

Line 205, “[17, 38]” was corrected as “[17, 42]”.

Line 211, “[39, 40]” was corrected as “[43, 44]”

Line 213, “[41-43]” was corrected as “[45-47]”

Line 217, “[44]” was corrected as “[48]”.

Line 229, “[45, 46]” was corrected as “[49, 50]”

4. Conclusions part:

Line 250, “a variety of experimental methods,” was added.

5. References part:

Line 300, “Hao W,” was deleted.


Line 390-452, The paragraphs (Line 54-60) in the introduction were transferred to the discussion, and sequence number in references is changed accordingly.