Author's response to reviews

Title: HLA class II allele polymorphism may influence susceptibility to adult dermatomyositis and polymyositis in a Han Chinese population

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Author's response to reviews:

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Dear Dr. Henderson:

We are grateful to the reviewers and editor for their additional comments and suggestions. The manuscript has been revised according to reviewer’s recommendations. The changes and our responses to reviewer’s comments are listed as follow:

Reviewer 1
Major Compulsory Revisions
Reviewer’s comments:
The fact that the frequencies of HLA-DRB1*04, -DRB1*12 and –DQB1*0303 in ILD show differences with controls but not patients who do not develop ILD is of concern. ILD is a complication of PM/DM. The primary level of genetic selection in these patients therefore is for genes which confer susceptibility to IIM. Within the patients who develop IIM there is further genetic selection for genes which confer susceptibility or resistance to ILD. It stands to reason therefore that if there are HLA genes which confer ILD susceptibility or protection these should be identified by comparing ILD patients with non ILD patients. The fact that differences cannot be seen when performing this analysis but can be observed when comparing with controls suggests this is a statistical quirk of the small numbers in some categories. This point should at least be acknowledged in the manuscript.

Authors’ response:
We thank reviewer for the comment and suggestion. Further analyses were
performed to compare frequencies of respective alleles and haplotype among those who developed ILD or dysphagia with those who did not. Results from further analyses confirmed the effects of HLA-DRB1*04 and HLA-DQB1*0303 on development ILD. Similar trends were observed for other alleles and putative haplotype between those with and without the complications, but the differences do not reach statistical significance. This is likely due to the small numbers of patients. This is acknowledged in the revision (Pages 7 and 8).

Reviewer’s comments:
The second last para of page 9 requires a change in the wording. It refers to DRB1*07 being a risk factor for DM while the same allele on another haplotype is a protective allele in Caucasians and African Americans suggesting it is a shared susceptibility allele across ethnic groups. It is not a shared susceptibility allele but rather shows opposing effects in different ethnic groups. The possible explanation for this effect needs to be discussed in the MS.

Authors’ response:
We thank the reviewer for the suggestion. The wording has been changed as suggested by the reviewer. The possible explanations for opposing effects are provided in the current version (Page 10).

Reviewer’s comments:
I still have concerns re the combined PM/DM group. It is claimed in the MS that PM and DM are distinct diseases with different genetic backgrounds yet the combined analysis is included on the basis that other groups have presented the data this way. None of the studied alleles were significantly increased or decreased in this group in table 2. In table 1 a comparison is made between PM and DM with respect to the occurrence of ILD. There is a significant difference between the groups yet they are combined into a single group with an expected frequency somewhere in between PM and DM. This provides no additional information, and in fact is not supported by any rationale. I would suggest that the PM/DM group be deleted with an explanation included in the MS.

Authors’ response:
The PM/DM group has been deleted from the tables and an explanation is included in the current version (Page 7).

Reviewer’s comments:
Discretionary Revisions
The functional unit of the DQA1 and DQB1 alleles is the DQ dimeric molecule. The authors do not wish to analyse the data with respect to DQA1, DQB1 combinations on the basis that their data suggests that DQA1 is involved in PM/DM susceptibility, while DQB1 is involved with ILD. Despite this analysing for combinations of these DQA1 and DQB1 alleles may enhance some of the associations and is more relevant to function.

Authors’ response:
We appreciate reviewer’s constructive suggestion. We plan to adopt this approach in the future to analyze new data (larger cohort data) collected from this ongoing project.

Reviewer’s comments:
The comment is made on page 10 that DM is likely to be induced by a humoral response while PM is more likely cell mediated. This statement needs to be discussed in the context of the greater frequency of autoantibodies in the PM group.

Authors’ responses:
In this revision, the greater frequency of autoantibodies in PM observed in our cohort and another study reported in the literature is discussed (Pages 10-11).

Reviewer’s comments:
Minor Essential Revisions
In the conclusion section The “D” has been left out of the DRB1 designation.

Authors’ response:
Correction has been made in the new version.

Reviewer’s comments:
To be consistent the word “putative” should be inserted in the heading to table 3.

Authors’ responses:
The word “putative” is inserted in the heading to table 3.

Reviewer 2
Reviewer’s comment:
I am happy with the stated changes that the authors have stated in their report. Please change HLA-RB1*04, HLA-RB1*12 in the conclusion to HLA-DRB1*04, HLA-DRB1*12.

Authors’ response:
Appropriate corrections have been made to the manuscript.

Reviewer 3
Reviewer’s comments:
The authors have not extended the patient and control cohorts and the differences between patients and controls did not reach significance after Bonferroni corrections. Therefore the information in the abstract is not correct as the authors should have included the corrected p-values.

Authors’ responses:
We appreciate reviewer’s comment. We also recognize that although our study is the largest study on Chinese PM and DM patients reported so far, this is still a
relatively small cohort. As discussed in the manuscript that caution should be excised to interpret the results derived from the study and the results are subjected for further validation by large cohorts. Nevertheless, we believe the data reported in the manuscript would provide useful information to the field.

In the current version, “corrected p (pcorr) NS” is included in the Abstract.

Once again, we are very appreciative to the reviewers for their thorough critique which we believe led to a much better manuscript.

Yours sincerely,

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