Author's response to reviews

Title: A single nucleotide polymorphism in TRAF1/C5 locus is associated with rheumatoid arthritis in a Han Chinese population

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Version: 4 Date: 14 June 2010

Author's response to reviews: see over
June 3, 2010

Scott Edmunds, PhD
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Dear Dr. Edmunds,

We would like to thank you and the reviewers for the constructive comments regarding our manuscript entitled “A single nucleotide polymorphism at the TRAF1/C5 locus is associated with rheumatoid arthritis in a Han Chinese population”) (MS: 1690918171343735). We have addressed the reviewers’ comments point by point below, which we feel have significantly improved the manuscript.

Reviewer #1

Major comments:
1 The rs2476601 SNP in PTPN22 has been reported to be not polymorphic in Asian populations. Moreover, several authors reported a lack of association with rs3761847 SNP in Asian and stated others polymorphisms in this locus with a most important role. What criteria did the authors take to select the polymorphisms under study? A more detailed SNP selection must be present in the manuscript.

Response:
1) Although Korean and Chinese populations are quite similar and rs2476601 was not polymorphic in Korean populations, the frequency of the risk A allele is 0.057 in HCB (Han Chinese Beijing) in the dbSNP129 database, and it was worthwhile to test this SNP in RA patients in a Chinese population. After all, Korean and Chinese populations are different, and this SNP has been robustly replicated associated with RA in many populations.
2) We selected the rs3761846 for an association study for RA patients in a Chinese population based on previous GWAS (Plenge et al. N. Engl. J. Med. 2007, 357, 1199-1209). We added this information in the manuscript.

2 As comment above, the role of rs3761847 SNP in susceptibility to RA in Asian is not clear since this SNP is not associated in Korean and in Japanese the susceptibility allele seem to be the opposite. This issue should be discussed in the manuscript.
Response: We agree with this point. We observed that rs3761847 A had increased the risk for RA in the present study, which is consistent with results observed in a Japanese population (Nishimoto et al. Ann Rheum Dis. 2010 Feb;69(2):368-73). However, this is the opposite of the original studies in Caucasian populations, in which rs3761847 A decreased the risk of RA. In addition, rs3761847 did not show a significant association with RA in the Korean population (Han et al. Arthritis Rheum. 2009 Sep; 60(9):2577-84). This indicated that rs3761847 may not be the true causative allele at the TRAF1-C5 locus (Lin et al. Am J Hum Genet. 2007 Mar;80(3):531-8.); thus, the true causative allele in this region needs to be further investigated. We added this information in the discussion section accordingly.

3 Since the importance of these loci in RA is well known and the relevance of this work is the new genetic background, more detailed Clinical information of patients should be included in order to see whether these data could be extrapolated to other populations and cohorts. This information is especially important since rs3761847 polymorphism has been reported to be associated with severity of RA.

Response: We agree with the reviewer’s point. All patients enrolled in this study at least two years after clinical diagnosis of RA, and the patients had five years of mean disease duration. We added this clinical information about the patients in the manuscript.

4 Although the sample size is enough for the case control study, authors do not have power enough in the anti-CCP and RF stratification study to fully exclude differences: “Our results further confirmed that rs3761847 in TRAF1/C5 was associated with RA in Han Chinese Asians, and this association does not depend on the concentrations of anti-CCP antibodies nor RF”. The lack of power in the stratification should be addressed.

Response: We corrected it accordingly.

5 PTPN22, TRAF1 and C5 are very important genes in autoimmunity. Therefore, a concise explanation of the role and whether the polymorphism studied could change its function should be important.

Response: In the discussion section, we added a concise explanation of the possible role of rs3761847 in altering the function of TRAF1 and C5 to cause autoimmune diseases, including RA.

Minor comments:
1 Typo error in page 8 second paragraph: “TSTAT4” should be STAT4.

Response: We corrected this typo.
2 Gene names must to be in italic.

**Response:** We corrected them accordingly.

Reviewer #2

Major compulsory revisions:
1 It is not justified why the two particular genes TRAF1/C5 and PTPN22 are chosen. It would strengthen the paper if, at the very least, the other non-HLA genes mentioned in the Introduction were also tested (STAT4 and TNFAIP3).

**Response:** We agree with the reviewer's point. Given that the association of STAT4 and RA in the Chinese population had been investigated (Li et al. Rheumatology (Oxford). 2009 Nov;48(11):1363-8.), we did not include a similar study in the present study. We would like to investigate the association of TNFAIP3 and RA in the Chinese population in a future study.

2 There is a considerable published literature, in addition to HapMap data available to indicate that R620W is, essentially, monomorphic or very rare in Han Chinese, meaning the study was very underpowered. It would have been better to include the aforementioned genes instead.

**Response:** We agree with the reviewer's point. R620W in PTPN22 was not polymorphic in Korean and Japanese populations in the previous studies, but this SNP was not investigated in the Chinese population, and the frequency of risk A allele is 0.057 in HCB (Han Chinese Beijing) in the dbSNP129 database. It was worthwhile to test this SNP in RA patients in a Chinese population. After all, Korean and Chinese populations are different, and this SNP has been robustly replicated and associated with RA in many populations. We would like to investigate other genes associated with RA in future studies.

Minor essential revisions:
1 The Table numbering is out of sequence.

**Response:** We corrected the numbering of the tables.

2 It would be helpful for the authors to confirm that the direction of association of rs3761847 is consistent with that observed in other studies.

**Response:** We observed that rs3761847 A increased the risk for RA in the present study, which is consistent with the results observed in a Japanese population (Nishimoto et al. Ann Rheum Dis. 2010 Feb;69(2):368-73); however, this is the opposite of the original studies in Caucasian populations, in which rs3761847 A decreased the risk of RA. This indicated that rs3761847 may not be the true causative allele at the TRAF1-C5 locus (Lin et al. Am J Hum Genet.
Thus, the true causative allele in this region needs to be further investigated. We added this information in the discussion section.

3 In Table 1, is it the allelic or genotypic P value that is presented?

Response: It is the allelic p value. We corrected the manuscript accordingly.

4 Why can't the data be presented in a consistent format between Tables 1 and 2 (Table 2 is better)?

Response: We edited Table 1 (now Table 2).

5 The last sentence of the first paragraph of page 9 doesn't make sense.

Response: We edited the sentence.

6 The paper could do with proof-reading.

Response: A native English-speaking colleague helped me copyedit the paper.

We wish to again thank you and the reviewers for the helpful comments, and hope that our revisions have appropriately addressed the reviewers' concerns and made the manuscript suitable for publication in the journal.

Sincerely,

Zhenglin Yang, M.D., PhD.