Author's response to reviews

Title: Association between insertion/deletion polymorphism in angiotensin-converting enzyme gene and acute lung injury/acute respiratory distress syndrome: a meta-analysis

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Author's response to reviews: see over
Editors of BMC Medical Genetics

Dear Sir:

We appreciate your email dated June 15, 2012 in which you informed us that our manuscript has been re-reviewed. The comments, our point-by-point responses to them, and changes made in the text (which are indicated by highlighting additions) are listed in following pages (i.e. deleted; black letter with line-through in yellow highlighted, incorporated; red letter in yellow highlighted, and corrected by native speaker; black letter in yellow highlighted).

Please note that we did not mark (highlight) the parts that “Edanz” modified for improvement of language quality, because these corrections, if we show all corrections in the manuscript, make it bothersome and difficult to read. We changed the name of our institution due to the recent renaming.

We sincerely hope that the changes made in the re-revised manuscript meet with the referee’s approval and, therefore, our manuscript is now acceptable for publication in your esteemed journal “BMC Medical Genetics”. If there are any further questions, please do not hesitate to contact us.

Sincerely yours,

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Responses to Reviewers’ Comments

Referee 1:

Reviewer: Carlos Flores
Reviewer's report:

The authors have addressed most points raised in my previous revision. However, there are a few issues that remain to be answered.

Minor essential revisions:
1. The authors have addressed one of the comments by including the following sentence in pages 5 and 15: “Since the genome-wide association study (GWAS) analysis of ALI/ARDS has never been performed, GWAS-accepted significance level of P value remained unknown.” However, this is not correct (see Christie et al. PLoS One 2012 for a recent GWAS of Trauma-derived ALI) and does not substitute the necessity of estimating the power of the study. In addition, current threshold for GWAS studies in complex diseases suggest threshold p-values in the range of 1.0E-08 (Pe’er et al. Genet Epidemiol 2008, 32: 381-5; Li et al. Hum Genet 2012, 131: 747-756).

Response: We thank the reviewer for the updated information about this topic. We deleted the corresponding sentences regarding GWAS study in the “Methods (page 4, line 5)” and “Discussion (page 13, line 7)” sections.

2. The authors have switched to a Bonferroni correction in this new version. While I am satisfied with their choice, I suggest the authors to control type-I error not only for the inheritance models and the two (three: all combined) populations, but also for the two traits (ALI susceptibility and mortality).

Response: We appreciate the reviewer for indicating our insufficient Bonferroni’s correction. We re-corrected P values as the reviewer’s suggestion. We revised and added the sentences regarding Bonferroni’s correction in the “Methods” and “Results” sections as follows;

“Methods” (page 7, line 4): Finally, Bonferroni’s correction was used to control the type I error rate in the meta-analysis of mortality. We employed 618 separate tests (three genotype models: allele, dominant, and recessive; three populations: total, Caucasians, and Asians; and two traits: susceptibility and mortality); therefore, we calculated the corrected P value by multiplying the original P value by 18. P was considered significant at less than 0.05.

“Results” (page 10, line 12): Moreover, the pooled OR remained significant after Bonferroni’s correction (corrected $P_{\text{allele}} < 0.0001$, corrected $P_{\text{dominant}} = 0.018$, corrected $P_{\text{recessive}} = 0.036$).

Discretionary revisions:
1. Please, substitute “electric” by “electronic” throughout the main text.

Response: We revised corresponding parts as the reviewer recommended.
Quality of written English: Needs some language corrections before being published

Response: We offered to copyedit this manuscript to improve language quality to “Edanz” which your journal recommended.

Referee 2:

Reviewer: Andy Overall
Reviewer’s report:

I have read the revised manuscript and the author’s comments. On the whole I am happy that the author’s have made a serious attempt at addressing the initial concerns raised. I have one Minor Essential Revision to request:

Under Statistical Analysis,
The employment of the Bonferonni correction needs to be clarified. Specifically, what significance level was used for each of the n analyses – alpha/n? The text does not make this clear.

Response: We apologize to the reviewer for our insufficient description of Bonferroni’s correction. We re-corrected P values as the reviewer’s suggestion. We revised and added the sentences regarding Bonferroni’s correction in the “Methods” and “Results” sections as follows;

“Methods” (page 7, line 4): Finally, Bonferroni’s correction was used to control the type I error rate in the meta-analysis of mortality. We employed 618 separate tests (three genotype models: allele, dominant, and recessive; 2 three populations: total, Caucasians, and Asians; and two traits: susceptibility and mortality); therefore, we calculated the corrected P value by multiplying the original P value by 18. P was considered significant at less than 0.05.

Minor typographical issues:
Abstract
“In addition, we [firstly] conducted” Delete [firstly]

Background
“severe form[,] acute” Delete [,]
“It is [well] suggested that the type and severity” Delete [well].
“So far, several variations in genes have been” Consider revising as “several genetic variants”
“while its polymorphism is consisted of the presence (insertion; I) and absence (deletion; D) of 287bp Alu repeat sequence in intron” Consider revising as “with a polymorphism that consists of.”
“Recently, strong evidence [have] been” replace [have] with “has accumulated”.
“Therefore the studies on association [remained] controversial” consider replacing with “remain”.
Statistical Analysis
“As the mode of ALI/ARDS’ inheritance [are] unknown” Replace with “is”

Results
“Four studies were conducted in Caucasians” consider revising as subjects of Caucasian ethnicity. Similarly for subjects of Asian ethnicity.
Control: Healthy control subjects
“However, the pooled OR derived from five [included] studies”
ACE I/D Polymorphism and the Mortality of ALI/ARDS

“Response: We revised all corresponding parts written above as the reviewer recommended to correct.

Quality of written English: Needs some language corrections before being published

Response: We offered to copyedit this manuscript to improve language quality to “Edanz” which your journal recommended.