Author's response to reviews

Title: Plasminogen Activator Inhibitor-1 4G/5G Polymorphism and Retinopathy Risk In Type 2 Diabetes: A Meta-analysis

Authors:

Tengyue Zhang (cynthia_zty@hotmail.com)
Chong Pang (pangpc2008@hotmail.com)
Ningdong Li (lnd30@163.com)
Kanxing Zhao (zkx4260@vip.163.com)

Version: 2 Date: 29 August 2012

Author's response to reviews: see over
Dear Editor D'Souza,

We would like to thank you for your consideration of our submitted article ‘Plasminogen Activator Inhibitor-1 4G/5G Polymorphism and Retinopathy Risk in Type 2 Diabetes: A Meta-analysis’ and the two reviewers for the insightful and constructive comments and suggestions, which have helped greatly to make the manuscript stronger. We carefully read their comments and suggestions and have tried our best to address all the comments/suggestions raised by the reviewers. We also conformed our draft to the journal style (for example, change the tables into portrait format). As you will see in the revised manuscript, thorough and extensive revisions have been made throughout the manuscript following the suggestions from the reviewers. The details of the changes can be found in the responses to the reviewers below and in the revised manuscript.

We hope you and the reviewers find the revised manuscript satisfactory and feel comfortable changing the article type to a technical advance. Thank you again for giving us the chance to review our work for publication in BMC Medicine.

Sincerely,

Tengyue Zhang

tengyue.zhang@yale.edu
Reviewer Daniel Petrovic:

**Comment 1.** A few information should be added regarding some additional candidate genes for DR.

Yes, we have listed part of the additional candidate genes for DR in Page 3, Background section, Paragraph 1, Line 4.

**Comment 2.** In Method section, data collection, line 5, the sentence should be written more clearly.

Thank you for pointing it out and kind suggestion. We have revised that sentence like this ‘For each eligible study, the following information was recorded: the first author’s name, the year of publication, country of origin, ethnicity, total number of subjects with DR and number of subjects without DR (DWR) as well as the DR/DWR distribution in each PAI-1 genotype.’ We also did some minor changes in Table 1 accordingly. We hope our expression can be clear enough for future readers.

**Comment 3.** Statistic should be checked by the statistician.

We conducted this analysis according to the standard meta-analysis methods. It is good for us to invite a statistician to check our meta-analysis. Unfortunately, we couldn’t find a statistician in limit time. Instead, we found an author who has published two meta-analysis papers (Su Lu) to review our statistical methods. At the same time, we double-checked our data and performed the analysis in software again. Now, we believe that there are no problems in our statistic and the results turn out to be obvious.

**Comment 4.** English language should be improved.

We felt very sorry for that. We checked many times ourselves and invited an English-native speaker (Elaine Zhou) to help us both correcting the spelling and grammatical mistakes and revising some sentences to improve our manuscript.

**Comment 5.** Few references could be added (ref 1-4).

Thank you for listing some necessary references for us. We have already enrolled them in our paper. You can find the first ref in Ref 9, second ref in Ref 3, third one in Ref 4 and the last in Ref 31.

Special thanks to you for your good comments.
Reviewer: Alisa Manning

As the reviewer said, although we have addressed in the discussion section, the available data set is somewhat small for a genetic association meta-analysis. As the limited data can be collected so far which we can do nothing to increase it, some minor changes in our sentences were performed in order to interpret our results more cautiously in this revision edition. We hope our meta-analysis results can raise a future interest to explore this gene’s relationship with DR by advanced methods.

Comment 1. For the statistical analysis, multiple genetic models and subsets of the data were considered and a P value of 0.05 for the summarized estimate was used to evaluate significance. Although the statistical tests are not independent, the authors should control for multiple testing or discuss this as a major limitation of the analysis.

Yes, indeed. As meta-analysis is a statistical method using multiple tests, it will increase the type I mistake and lead to a false positive result. Thus, ‘possible’ relationship was emphasized again in the limitation part. We discussed this as our first limitation in Page 11, Paragraph 2, Line 2.

Comment 2. In this analysis, only marginal significant associations have been found—there are no genome-wide significant findings. Some may argue that genome-wide significance is not needed because only one genetic polymorphism is being tested. Please add a discussion relating this genetic association with the particular effect size to other genetic findings for DR of similar effect size. This will allow the reader to put the PAI-1 4G/5G polymorphism in context.

Thank you very much for your kind suggestion. To emphasize the significance of our manuscript, we added nearly a whole paragraph at the beginning in our discussion section before summarizing our results by reviewing the current situation in GWAS research in DR and the meta-analysis of other genes’ polymorphism (Page 8, Last line). We also supplemented our discussion in the third paragraph regarding the possible explanation to our results (Page 11, Paragraph 1, Line 2). We hope our revision under your good suggestion can make our paper stronger and solid in context.

Comment 3. The manuscript should be reviewed and edited by an English speaking individual.

We felt very sorry for that. We checked many times ourselves and invited an English-native speaker (Elaine Zhou) to help us both correcting the spelling and grammatical mistakes and revising some sentences to improve our manuscript.

Comment 4. In Table 1, the population of the Pima people is located in the United States. Table 1 should be double-checked for accuracy.
We apologize for this mistake. We have corrected it in our new manuscript. We also double-checked the draft to make sure other information was correct. Thank you! Additionally, some changes were made in this table to make information clearer to the future readers.

**Comment 5.** In Table 2, the number of individuals contributing to each test should be included.

Thank you for your comment. We changed the format of Table 2 and the information of Alleles/Genotypes of each test was added.

**Special thanks to you for your good comments!**

Finally, we express our sincere appreciation to the reviewer for his/her efforts in improving the quality of this manuscript.