Author's response to reviews

Title: Associations of Complement Factor B and Complement component 2 Genotypes with Subtypes of Polypoidal Choroidal Vasculopathy

Authors:

Koji Tanaka (tanaka.koji@nihon-u.ac.jp)
Tomohiro Nakayama (nakayama.tomohiro@nihon-u.ac.jp)
Ryusaburou Mori (ryu-m@sa2.so-net.ne.jp)
Naoyuki Sato (n-satou@hsri-ei.co.jp)
Akiyuki Kawamura (kw-eye-c@xb3.so-net.ne.jp)
Mitsuko Yuzawa (yuzawa.mitsuko@nihon-u.ac.jp)

Version: 3
Date: 3 May 2014

Author's response to reviews:

May 3, 2014
Editor-in-Chief
BMC Ophthalmology

Dear Editor,

Enclosed is the revised version of our manuscript entitled “Associations of Complement Factor B and Complement component 2 Genotypes with Subtypes of Polypoidal Choroidal Vasculopathy” (reference ID number 6905275981236409R1), which we are submitting for possible publication in BMC Ophthalmology.

We appreciate the review of our previous submission of this manuscript and the helpful comments sent on April 15, 2014. We have revised the manuscript based on the reviewers’ comments and have enclosed a list of responses and the changes made.

My coauthors and I believe that our revisions adequately address all of the concerns raised by the reviewers, and hope that the revised manuscript is now suitable for publication in BMC Ophthalmology.

Sincerely yours,

Tomohiro Nakayama, M.D.
Division of Laboratory Medicine, Department of Pathology and Microbiology
Nihon University School of Medicine
30-1 Ooyaguchi-kamimachi, Itabashi-ku, Tokyo 173-8610, Japan
Tel.: +81-3-3972-8111 (Ext. 8205); Fax: +81-3-5375-8076
E-mail: nakayama.tomohiro@nihon-u.ac.jp
To Reviewer #1

Thank you very much for your helpful comments. We have revised our manuscript accordingly. Revisions are underlined in the text.

#1 Reviewer’s comments
1. In this manuscript the authors have demonstrated differences in the association of certain C2-CFB SNPs between two angiographic subtypes of PCV. The study was well conducted and the results were quite interesting. I have just few comments for better understanding of this paper.

Minor essential revisions
1) Was the cohort in this study largely same as the one in the authors’ previous study or newly enrolled?
2) Page 7, line 15: Does “minor allele frequency” mean “minor allele homo frequency”?

Discretionary revisions
1) The author previously reported that CFH variants were similarly associated with polypoidal CNV and typical PCV. However, the present study demonstrated that C2-CFB variants were associated differently between these two PCV subtypes. It is very interesting that complement pathway may affect the formation of PCV subtypes in very complex manner. Do the authors have any idea to explain this?

Response:

#Essential revisions
1) This cohort is the same as that in our previous study. We researched the other SNPs in this study after obtaining written informed consent from every enrolled patient.
2) “minor allele frequency” meant “minor allele homozygous frequency. We revised accordingly.

#Discretionary revisions
1# We do not know how the complement pathway affect PCV subtypes.

However, we offered our speculations on Page8, line 25- Page9, line 2. PCV showed less inflammation than tAMD. We believe that typical PCV can be discriminated from other forms of AMD.

To Reviewer #2
Thank you very much for your helpful comments. We have revised our manuscript accordingly. Revisions are underlined in the text.

#2 Reviewer’s comments
1. The author presents a genetic association study to assess whether C2 AND CFB genotypes were associated with subtypes of PCV in a Japanese cohort. They found some genetically difference between polypoidal CNV and typical PCV. However, the author didn’t perform the statistical analysis in a correct way. They use 2*2 contingency tables and 2-sided Fisher’s exact test to calculated distribution of alleles and genotypes respectively. In this way, at least Bonferroni method should be used to correct the multiple comparisons. After corrections, some p values may become insignificant.
Since the author assumed that polypoidal CNV were genetically and histopathologically close to tAMD, it may be better to supply the statistic data of the four SNPs in tAMD patients. Moreover, the author may need to state clearly the meaning of differing polypoidal PCV from tAMD.
In addition, the results of the typical AMD study should be provided to make the article more persuasive.

Response:
#1) We provided the results for tAMD in Tables 1-3 and also used the Bonferroni correction in Table 2 and Table 5. Some p-values became insignificant, but this study remains valuable. We performed a logistic regression analysis for the individual SNPs and assessed the results after adjusting for confounding factors (Table 6). The p-values were set below 0.05. We believe this level for p-values to be appropriate. This level was applied in our previous case-control studies (#1, #2)

#1

#2

2) We added the meaning of the difference between polypoidal CNV and tAMD on Page7 line 27- Page8 line 1