Author's response to reviews

Title: The transcription factor 7-like 2 (TCF7L2) polymorphism may be associated with focal arteriolar narrowing in Caucasians with hypertension or without diabetes: the ARIC Study

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Author's response to reviews: see over
March 05, 2010

Re: 1333521461299504 - An association between the transcription factor 7-like 2 (TCF7L2) polymorphism and focal arteriolar narrowing in Caucasians with hypertension or without diabetes: the ARIC Study

Dear Dr. Alam,

We greatly appreciate the careful review of our manuscript and are glad that you would like to consider our revised manuscript for publication. We would like to thank the Reviewer, Dr. Stéphane Cauchi, for constructive and helpful comments. We have made revisions based on the comments we received and will briefly highlight these points below.

REVIEWER’S COMMENTS TO AUTHORS:

1. The number of studied subjects was clearly different when comparing Caucasians (N = 8121) and African Americans (N = 2199), Caucasians with (N = 1206) or without diabetes (N = 6915), people with (N = 3185) or without hypertension (N = 4936). For this reason, it’s difficult to estimate what is due to true effects and due to power issues. Although the authors acknowledged the limitations of their study in the Discussion section, it’s necessary to calculate the statistical power for each analysis (in supplemental material) to let the reader know what the level of confidence is (either for negative or positive results).

We thank the reviewer for this suggestion. The power plots were added as Supplementary Materials “Additional materials for the outcomes of retinal microvascular lesions and caliber, by race and/or by hypertension/diabetes status”, as suggested by the reviewer. In the 3rd paragraph of the Discussion section where we discussed the limited power, the additional file on power analysis was referenced explicitly by the file name “See additional file 1: Power Analysis on the associations between TCF7L2 rs7903146 and retinal microvasculature in the ARIC Study”.

2. This study is the first to examine the association with retinal microvascular lesions and caliber, so multiple-testing corrections should be applied in order to avoid false-positive results. When applied, TCF7L2 is not associated with focal arteriolar narrowing anymore. So, as a precaution I would change the title into “The transcription factor 7-like 2 (TCF7L2) polymorphism may be associated with focal arteriolar narrowing in Caucasians with hypertension or without diabetes: the ARIC Study”.

We thank the reviewer for this suggestion.
We thank the reviewer for this suggestion. Now the manuscript title has changed to “The transcription factor 7-like 2 (TCF7L2) polymorphism may be associated with focal arteriolar narrowing in Caucasians with hypertension or without diabetes: the ARIC Study”, as suggested.

3. In the Introduction and Discussion sections, I would not report the odds ratio (although published in BMC Medicine) because only one CC subject had diabetic retinopathy in the inChianti paper. Furthermore this OR is based on a recessive model overestimating the association with retinopathy whereas the most likely inheritance model was found to be log-additive for type 2 diabetes.

We agree with the reviewer on this comment. Now the odds ratio and 95% confidence interval (odds ratio=7.15, 95%CI=0.87-58.51) have been removed from the Introduction and Discussion sections.

4. In the Results section, the authors stated that age, fasting glucose and prevalence of diabetes were different between Caucasians carrying different TCF7L2 genotypes. What about HDL levels?

We thank the reviewer for this comment. As shown in Table 1, HDL-C levels were marginally different between rs7903146 genotypes in Caucasians. We revised the wording in the Results section as follows: “No statistically significant differences in demographic or behavioral characteristics (sex, and current smoking) were noted by genotype status except for age (P=0.03) and HDL-C levels (P=0.05) in Caucasian participants (Table 1)”.

5. In another ARIC study, Tikellis and colleagues (American Journal of Hypertension, 2008) observed that African Americans with generalized and focal retinal arteriolar narrowing were more likely to have left ventricular hypertrophy. Did you observe similar features in Caucasians carrying the TCF7L2 risk allele?

In this study, we did not look at left ventricular hypertrophy. As indicated in Tikellis et al. 2008 paper, “Echocardiograms were conducted only in African-American participants residing in Jackson area with echocardiograms being read by one cardiologist”, thus we do not have the echocardiogram data in Caucasians.

6. Reference 7 should be updated

We thank the reviewer for this comment. Now the reference 7 has been updated as follows:


7. Please report exact P values

We thank the reviewer for this comment. In Table 1, we updated the P values from <0.01 to <0.00001 for prevalent diabetes and from <0.01 to 0.00002 for glucose levels in Caucasians.
Thanks again for the careful review of our manuscript. If you have any questions, please call me at (919) 966-2148 or email me at knorth@email.unc.edu.

Sincerely,

[Signature]

Kari E. North
Associate Professor