Reviewer's report

Title: 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

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Reviewer: Stéphane Cauchi

Reviewer's report:

TCF7L2 has been extensively studied in the ARIC study (Folsom et al., Diabetes Care, 2008; Bielinski et al., Diabetologia, 2008; Köttgen et al., J Am Soc Nephrol., 2008; Yan et al., Diabetes, 2009). In this manuscript, Yan and colleagues analyzed the possible association between the TCF7L2 rs7903146 T allele and retinal microvascular signs. No consistent association was observed. However, the authors detected a nominal association with focal arteriolar narrowing in Caucasians with hypertension or without diabetes. This study was well conducted but I have few comments:

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).

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"

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.

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?

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?

6) Reference 7 should be updated

7) Please report exact P values

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests