Reviewer's report

Title: Sequence variation in telomerase reverse transcriptase (TERT) as a determinant of risk of cardiovascular disease: the Atherosclerosis Risk in Communities (ARIC) Study

Version: 1 Date: 31 October 2014

Reviewer: Sebastien Theriault

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Minor Essential Revisions

1) The background section in the Abstract should be shortened.

2) More information should be added to the methods section in the Abstract: mention that SNPs were genotyped and how, add mortality to the outcomes.

3) Add 95% confidence intervals to the hazard rate ratios in the Results sections of the Abstract and of the manuscript.

4) Clarify the objectives at the end of the Background section: precise why the 6 SNPs were selected (closed to / on the TERT gene, including the one previously associated with telomere length…), add mortality to the list of outcomes.

5) In the Methods section, precise the definition of stroke – it is not clear how ischemic strokes were identified / separated from hemorrhagic strokes (imaging?), what was the proportion of patient with imaging available?

6) Clarify how the 6 SNPs were selected – were they all in the TERT gene, if not were they all within a certain distance? Were all SNPs within that distance included? (second paragraph, Methods section).

7) What does “European Americans” mean in the Methods section, end of second paragraph? Was Hardy-Weinberg equilibrium verified in all ethnicities?

8) Describe the models chosen in the statistical analysis section – variables should be clearly stated and differences between outcomes should be explained (variables for model 2 are not the same in the table legends).

9) In the last paragraph of the Results section, the first part of the sentence at line 221-222 should be in the Introduction or Methods section instead.

10) There is an error in the name of the SNP at line 250 (third paragraph of Discussion), it should be rs2853668 instead of rs285366.

11) The authors should try to explain the discrepancy between their results and the WHG study for rs2853668 (protection vs increased risk) – related to the different ethnicity? Was this SNP linked to shorter or longer telomere length in
any previous study?

12) At the end of the Discussion, other genes associated with telomere length are mentioned, is there a reason why SNPs in those genes were not tested for association with CVD and mortality in the current study (were they available on the array)? Why choose only TERT?

13) In the Conclusion, it is speculative to imply that the study suggests that the genetic variations reported “may contribute to the etiology” of cardiovascular disease, “may be associated” would be a better formulation.

14) In Table 2, the third and the fourth SNPs were inverted for White – impairs readability.

15) The variables in model 2 are not the same depending on the outcomes (alcohol and cholesterol are only in some - legends of the tables), is that a mistake – why would the authors chose to adjust for different variables (see point 8)?

Discretionary Revisions

1) False-discovery rate analysis and power calculation could be performed to help in the interpretation of the results.

2) The Discussion could be shortened, the second paragraph includes a part that is repeated in the Background and the fourth paragraph includes a lot of details for what appears to be a secondary outcome in the study (mortality).

3) The authors could mention in the limitations that telomere length was not measured, which limits the interpretation of the findings in terms of explaining the link with cardiovascular disease.

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.