Reviewer's report

Title: rs1234313 and rs45454293 are risk factors of cerebral arterial thrombosis, large artery atherosclerosis, and carotid plaque in the Han Chinese population: a case-control study

Version: 0 Date: 19 Nov 2018

Reviewer: Jun Young Chang

Reviewer's report:

The authors intended to evaluate the association of TNFSF4 SNP (rs1234313 and rs45454293) and the risk of atherosclerosis by conducting prospective case control study. The surrogate markers for atherosclerosis in this study are calcification, thickness, and multiplicity of the plaque. Prior studies could not find any association between TNFSF4 polymorphism and ischemic stroke.

1. According to the study, the genotype and allele frequencies of TNFSF4 SNP (rs1234313 and rs45454293) seemed to be not significantly different between the case and control groups. The association of TNFSF4 polymorphisms (rs1234313 and rs45454293) and carotid plaque features were compared only within the case group. The association of TNFSF4 polymorphisms (rs1234313 and rs45454293) and carotid plaque features between the case and healthy control needs be mentioned first. Also a cut off level of statistical significance needs to be corrected by multiple comparisons.

2. The definition of calcified plaque (signal with strong echo) is ambiguous and needs to be clarified. The presence of carotid plaque calcification only does not represent a plaque vulnerability. Rather than calcification, plaque features including irregular, ulcerative surface, echolucent core and thin fibrous cap, are associated with future ischemic stroke events. The association between TNFSF4 polymorphisms and vulnerable plaque features seems more clinically meaningful.

2. The definition of thick plaque (maximal carotid plaque thickness>1.9mm) is somewhat arbitrary. Sensitivity analysis using another index of atherosclerotic plaque burden including total plaque area calculated by the sum of areas of all plaques seen, or plaque thickness as a continuous scale needs to be performed to clarify the association of rs45454293 SNP and subsequent risk of ischemic stroke.
3. According to the methods, the authors matched the control using age and gender, but table 1 showed significant differences in age and gender between the case and control. The reason of the imbalance needs to be explained.

4. Regarding the Inclusion criteria in this study, enrollment period, definition of acute ischemic stroke including acute period, confirmation of ischemic stroke by MR needs to be mentioned. The reason why patients with atrial fibrillation were excluded is not clear. If the authors intended to include the acute ischemic stroke with large artery atherosclerosis, the criteria also include that point. Dysfunction of heart/lung/kidney needs to be clarified more clearly and the reason for exclusion should also be explained.

5. There was a substantial loss of case subjects due to absence of basic information. The characteristics of the patients who did not included in the analysis needs to be mentioned also.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

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