Reviewer’s report

Title: Peripheral blood gene expression signatures which reflect smoking and aspirin exposure are associated with cardiovascular events

Version: 1 Date: 20 Nov 2017

Reviewer: Bradley Ander

Reviewer's report:

The authors conduct a study on peripheral blood of subjects in the PREDICT trial examining expression of genes related to platelet reactivity on aspirin (ITGA2B) and smoking status (sGES panel of five genes). The study builds upon previous work of the group that developed smoking and platelet reactivity associated genes, and links these with major adverse cardiac event outcomes (MI, stroke, and death). Here, they find ITGA2B expression is higher in females than males, validate their previously identified sGES. The expression levels of these genes was used to run through logistic regression for association with MACE. The two measures, alone or combined, were associated with MACE, with slight advantage taken together.

Smoking has a powerful inflammatory and elevates oxidative status in patients. It is important to understand the differences that affect a large proportion of patients. Further, predictive risk of MACE based on measurable expression criteria is useful in theory, but may not represent much advantage over simple self-reporting or categorization of aspirin use or smoking status. However, self report can be flawed and inaccurate, so more reliable indicators of assessing and communicating risk are warranted.

Overall, the study is well conceived and presented in a clear fashion. Some further clarifications should help myself and other readers better understand the findings related to ITGA2B. In particular, it is somewhat confusing fitting the ITGA2B results into the context of risk and smoking status. In response to aspirin, platelet response decreases and ITGA2B is elevated, reducing MACE (left side of figure 3). Smoking elevates the sGES, increases platelet reactivity, and drives down ITGA2B (right side figure 3). Overall, the group finds increased ITGA2B is elevated and associated with MACE (as surrogate for ARS). But in the case of smokers, ITGA2B expression is down. These overall findings are stated in a clear manner on their own, but somehow when put into figure 3 become confusing. Ensuring the key findings of the study are communicated clearly is essential.

Strengths

- The PREDICT cohort is a robust set of patients to study.
- The technical approach, analyses and reporting is sound and well-presented.

- The authors have overall written with high quality and present a thorough discussion of the work in the context of the field and related studies.

Weaknesses

- Figure 3 is confusing in the way it tries to summarize the overall findings (see below). Perhaps clarification or an adjustment can be made so it can concisely summarize the findings. The point that it illustrates elevated ITGA2B as inhibiting/decreasing MACE seems to go against the work presented and the bullet points are not clear.

Specific Points

- Page 5, line 47 - patients self report smoking status as never, former or current. Are only "current" used in the study as table 1 would seem to indicate?

- Table 4 - what is SMK? Is it GES? Or sGES?

- Figure 3 - The second bullet point text is confusing. "Regulated in an opposite fashion" is oddly and confusingly phrased. Perhaps they mean "inverse fashion"?

- Figure 3 - "counteract" is one word

- Figure 3 - Third line - the illustration indicates higher ITGA2B should be lower risk?

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

Yes

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

Yes

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:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal