Reviewer's report

Title: Fatty acid binding protein 3 (FABP3) is associated with insulin, lipids and cardiovascular phenotypes of the metabolic syndrome through epigenetic modifications in a Northern European family population

Version: 5 Date: 21 January 2013

Reviewer: Reid S Alisch

Reviewer's report:

This is a study testing whether DNA methylation variation at the promoter of FABP3 is associated with metabolic syndrome phenotypes. The findings from this study are suggestive and may have important implications for cardiovascular disease; however, the current version lacks a clear connection to FABP3 expression and methylation within the heart (the tissue of interest).

Major Compulsory Revisions:

1. In the "Response to the Reviewers" the authors informed us that they removed the EMSA results in lieu of the expression data. However, the authors have included the EMSA findings in both the abstract and the discussion (below), but fail to include it in the results section. I assume that this was an oversight and expect that the authors will either remove the EMSA findings from these sections or will fully describe them in the results section. I'd vote for it's inclusion in the manuscript but it needs to be explained better than it was in the original draft.

Abstract:

"Further, we show that differential methylation of FABP3 affects binding activity with nuclear proteins from heart tissue."

Discussion:

"We also found that differential methylation at these units affects the affinity of this region of DNA for binding to nuclear proteins extracted from human heart, thus indicating a possible mechanism by which methylation may regulate gene-expression in this region."

2. Since the authors are using the expression data to demonstrate a correlation between FABP3 expression and MutS phenotype, and by association FABP3 methylation level and MutS phenotype, it would help to convince me of a correlation if the authors included any correlative observed between methylation level and expression (i.e. does promoter methylation associated with a MutS phenotype correlate with lower FABP3 expression level and that same MutS phenotype?).

Minor Essential Revisions:

3. The rationale described in the first paragraph of the conclusion seems more
appropriate for the introduction to help the reader better understand the approach.

4. It is not clear in the "Results" section or the "Discussion" that the cohort used for the expression studies is different from the cohort used for the methylation studies. This should be made clear. We also need to see the demographics of this cohort in a table.

5. Please make sure to include all "results" data directly into the manuscript, especially for major findings. For example; author wrote, "The strongest association was that between overall average methylation and total cholesterol level," yet they did not include the significance level, requiring the reader to refer to Table 2.

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

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I do not have competing interests.