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

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Reviewer: David Serre

Reviewer's report:

This is a potentially interesting study testing whether DNA methylation variation at the promoter of FABP3 is associated with metabolic syndrome phenotypes. The study design and the use of family-based approaches is novel and appropriate for the question investigated. I especially appreciated the inclusion of heritability analyses.

Major Compulsory Revisions

1- The authors perform a large number of tests but seem to correct only for the number of CpG tested (N=17 or 18), not for the number of phenotypes (N=42) (page 13). The actual number of tests performed is at least 714 (42*17) and needs to be corrected for.

2- The effect sizes observed are very small (<2%) and it is not obvious to me that these are meaningful clinically or biologically. This should be more extensively discussed (displaying sex average would for example help understanding whether methylation levels are indeed "strongly affected by sex"). The authors should also try to refrain to use "strong" and other adjectives to qualify these correlations.

Minor Essential Revisions

3- it is not clear whether all 517 individuals were assessed for DNA methylation and if this was done in triplicates (page 7). If multiple replicates were performed, how similar were they?

4- the authors state in the abstract and introduction (page 5) that FABP3 "transcript levels in PWBCs are correlated with MetS leading components". They never use these data in their study. I would like to see some correlations between FABP3 methylation and gene expression (which would be much more convincing that the EMSA experiment presented).

Discretionary Revisions

5- claiming that peripheral blood DNA methylation is highly correlated with that of other tissues is a bit shaky given the amount of data emphasizing tissue-specific methylation patterns. Why not directly show from the heart tissue used in the EMSA experiment that the pattern of methylation at the FABP3 promoter are similar (or not) in heart and PWBC?
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:

No competing interests