Reviewer's report

Title: Integrative network analysis reveals different pathophysiological mechanisms of insulin resistance among Caucasians and African Americans

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Reviewer: Petter Storm

Reviewer's report:

This study examines the transcriptomes from adipose tissue in African americans (AA) and compares it to Caucasians (CA) and relates findings to metabolic phenotypes. Two approaches are taken; first they identify genes DE in relation to the phenotypes and associate these with pathways and biological process. Secondly, a data driven approach is taken to identify gene modules that are then further characterized.

Major Compulsory Revisions

The paper is very well written and easy to follow. The flow is perfectly logical and overall I am quite optimistic about this paper.

However I have two fundamental criticisms:

1) No validation of the results are performed (save for technical validation using qPCR) using alternative data sets/methods. This makes the paper descriptive and lowers my enthusiasm for the results. If alternative methods (for example metabolomics) has been performed on the data set and can be related or, alternatively, the gene sets identified in this paper can be tested for association in separate data sets that would greatly strengthen the paper.

2) The “integrative network approach” is given a lot of focus in this paper. I think the justification for this type of method and its applicability in this paper is lacking.

Major criticisms of technical nature:

3) Is the data deposited in a public repository?

4) It is surprising to this reviewer that the overlap in transcriptional response in relation to SI is so small comparing AA vs CA (Figure 2). For example only 800 genes are shared whereas 2400 genes are unique to either group. Has the authors excluded every possible alternative explanation?

Minor criticisms

5) A number of hypothesis are tested throughout this paper and it is quite dense in p-values. Could the authors please clarify on how correcting for multiple testing was performed.
6) The data is adjusted for using age and gender. Data driven identification of covariates using eg. PEER could help.

7) There is quite an unbalance in number of AA and CA participants. This not addressed/discussed adequately by the authors.

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 declare that I have no competing interests