Reviewer's report

Title: Gene Regulatory Network reveals Oxidative Stress as the Underlying Molecular Mechanism of Type 2 Diabetes and Hypertension

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Reviewer: Dwaipayan Bharadwaj

Reviewer's report:

The authors have tried to build a gene disease integrated network model of interactions between the genes differentially regulating the various inflammatory diseases such as type 2 diabetes, hypertension, and obesity. The molecular mechanistic interrelations among these complex diseases were explored through pathway analysis approach. The model analysis integrated the computational studies and available database sources for genes and protein information which revealed the oxidative stress mediated regulatory cascade as the linking hub for the pathogenesis of T2D and hypertension.

The experimentation has been well researched and the data was mined through authentic bioinformatics data sources. The authors took care of considering the experimental validity of the interaction data. A systematic approach was adopted in the development of the model.

The ideology of considering the genetic interactions of co-related diseases and creating a network hub inclusive of the protein interactions which provides the points of common interaction can unveil the common ‘landmarks’ which has been not identified through genetic and functional studies yet.

However, some concerns which came across while evaluation of the manuscript are as follows:

1. The author mentioned the phrase “understanding the underlying molecular mechanisms of obesity-induced insulin resistance” in the background section. This implicates that the model analysis is being focused solely on the insulin resistance caused due to obesity factor and excluding other possible factors. Thus the study will be biased as the source.

2. The CVD gene cascade has not been included in the network model. The oxidative stress mediated regulation cascade has been linked with CVD whereas there is no relative study for the same in the manuscript.

3. The type 1 diabetes has been studied and molecular linkage established through the PPI patterns under the results section but is nowhere mentioned in the methods section. Also, the aim behind establishing the linkage among T1D with other diseases is missing.

4. There are recent available literatures on gene predicting/prioritization methods.
to unearth the genes for complex diseases (like obesity/T2DM) based on protein interactions and network analysis. Authors should compare their predicted integrated network model to those.

5. Since in the conclusion authors are giving importance of biomarker identification it would be better to determine false positive percentage using simple ROC curve.

6. Figure 5, Figure 9 can easily go the supplementary tables as they are not adding any added advantage during reading the manuscript.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'