Reviewer #1: This is an interesting and useful analysis for a field where significant gaps in knowledge exist. The current analysis may be able to pinpoint some critical mechanisms and should stimulate further research. The following minor points and suggestions should be considered in a minor revision:

Response: Thank you for the comments and the helpful suggestions.  
  
Page 1- The "Lejeune Machine" - please include some references here

Response: We have included 2 references as suggested

page 2: Type I error a space is missing

Response: Corrected  
  
Page 2 "should be" should be "needed to be"

Response: Corrected  
  
Page 3 'expression' is misspelled

Response: Corrected  
  
Results First Para: it would be interesting to show the distribution of these 1003 and 912 genes how they are distributed on various chromosomes. The names of all these genes would be also useful in a supplemental table.

Response: We have added this information in the revised paper (Suppl 1).  
  
Results: you already abbreviated DS, don't use the full term again

Response: Corrected  
  
CBS: beta should be in greek symbol

Response: Corrected  
  
Discussion first para: rephrase "mitochondrial complexes activities" and "of note that out"

Response: Both sentences have been rephrased and improved  
  
P9: one "and" should be de italicized

Response: Corrected  
  
P9: the following paper might be interesting to review and discuss...how the suppression of one complex can affect the expression of others:  DOI: 10.1016/j.mito.2007.02.001

Response: We have added this information in the revised paper  
  
The Discussion should be better integrated with the prior meta analysis paper of the authors. For mitochondrial function, the discussion is OK, because here the function of the mitochondria is also dependent on soluble factors like H2S as discussed. But for the glycolytic intermediates, and for citric acid cycle and lipid mediators, authors could look at the meta analysis of the metabolites in the other review to check if the up or downregulation of some rate limiting enzymes correlate with the increase or decrease of the respective substrates and products. This exercise should be performed for a selected number of key regulatory genes identified (not necessarily all of them).

Response: We have selected a number of genes/pathways and added this information in the revised paper. Please note that in most cases the gene expression studies, the available metabolomic studies and the available proteomic studies have been obtained from different cells/materials, which makes the cross-interpretation of these alterations difficult. Nevertheless, we have tried the best we could in this respect (and we are discussing the limitations of such approach).  
  
Also, if there are any proteomics studies performed in DS, it could be interesting to check if the mRNA regulation corresponds to protein regulation (some cases are discussed in the manuscript where such correlation does not exist, but maybe there are other instances where mRNA is increased and a prior published paper shows that also the corresponding protein is increased?

Response: We have selected a number of key genes and performed the suggested analysis and this is now added to the revised paper  
  
Reviewer #2: Pecze and Szabo performed a meta-analysis to evaluate the alterations of which pathways can be found from the changes in gene expression observed in individuals with DS reported in two public repositories. The approach described and the scientific question are very sound and scientific relevant, however there are several issues (including language limitations) that weaken the overall significance of the study.

Response: Thank you for the comments and the helpful suggestions.

First of all, the Authors do not clearly state the overall goal of the study in the introduction (including the criteria used for choosing the analyzed pathways). As it is, the intro is not exhaustive as it does not set the hypothesis of the analysis in the context of the knowledge gaps existing in the field. Also, the final part of the intro feels also out of place. Albeit the clarification of the approach adopted needs is a nice support to the reader, the specification of Type I and Type II error in this context does not feel needed.

Response: We have carefully reviewed the introduction and we feel that the main goal is stated as to conduct a meta-analysis to identify key expression patterns in DS especially related to mitochondrial pathways. We also state the means to this goal (i.e. a meta-analysis), and we feel that the general explanation of how a meta-analysis can reduce Type I errors as well as Type II errors is a valid part of this justification. We have simplified this latter part, but we feel that complete deletion of it is not justified.

Also, the presentation of the results is not effective. Indeed, results sections should report the actual findings instead of illustrating the significance of the chosen pathway or explaining the mediators analyzed. May be some of this can be moved to the intro.

Response: This suggestion is difficult to follow, because this would mean that the Intro would have to explain the core characteristics of all biochemical mechanisms that we cover in the meta-analysis. We feel that a brief introduction of these pathways is better placed in the section where it is now. Please note that the Results section is actually a combined Results and Discussion section, precisely for the above reason (i.e. better integration of the findings of the metaanalysis and the interpretation of the findings). Therefore, we start each section with a short explanation of the context of the pathways analyzed, followed by the changes in DS as identified by metaanalysis, and finally some additional discussion on the implications of these changes. Please note that the other Referee did not have a systematic problem with this approach. However, the other Referee has suggested that we also include additional analysis to check how the gene expression patterns are associated with metabolomic or proteomic alterations in DS. We have selected several genes/pathways for this and have now included this analysis in the revised manuscript.

The titles of the results paragraphs are often inappropriate, just to cite one: "There are significantly up or downregulated genes in glutamate metabolism". Also, "DS induces a significant dysregulation of multiple genes of the citric acid cycle", may be better to state that "DS is associated with". In the paragraph "Genes involved in oxidative phosphorylation are mostly downregulated in DS" the Authors start with a very generic sentence: "Five genes related to oxidative phosphorylation were detected to be upregulated and these were the following". Although the title of the paragraph refers to individuals with DS sentences should be clear as standalone.

Response: We have revised the titles in he revised paper as suggested and have improved the sentences that are mentioned in your comments.

Minor points:

The title has the repetition of the word alteration that feels redundant.

Response: Corrected

Page 7: "Of note that". Please consider having the manuscript revised by a native English-language speaker.

Response: This sentence was corrected, as well as several others for style and presentation