We thank the reviewer and editor for considering our manuscript. We have substantially modified the manuscript to reflect these comments and suggestions as described below:

Reviewer #1: The manuscript PONE-D-14-30128 entitled “Gene Expression Signature in Adipose Tissue of Acromegaly Patients” by Hochberg et al. describes the analysis of the adipose tissue transcriptome form acromegaly patients vs. non-functioning adenoma patients, which revealed drastic changes in previously and newly identified targets related to metabolism, insulin and lipid pathways.

The rational of the study seems to be appropriate and well defined; however there are major study and technical limitations that lessen the relevance and impact of the study. It seems that the manuscript do not describe a technically sound piece of scientific research. It is not clear if the experiments have been conducted rigorously, with appropriate controls, replication, and sample sizes.

Regarding the study design, it seems that non-functioning pituitary adenoma patients are not the appropriate controls in this study as they are not normal, healthy controls. Indeed, non-functioning pituitary adenoma patients can present several hormone dysfunctions and other comorbidities that could be impacting adipose tissue biology.

**Our opinion is that the non-secreting adenoma controls are technically a reasonable control, relative to “normal” controls. These samples are collected by the same surgeons using the same techniques and were processed identically. Furthermore these patients, even if not well age matched, do still have a pituitary tumor so we are controlling for this factor. To the concern that the non-functioning adenoma is phenotypically altering the physiology of these patients we propose to both mention this as a potential issue we have mentioned this as a caveat in the discussion with the following text:**

**One potential caveat to our approach is the use of patients with a non-secreting adenoma as the control group. It is possible that these adenomas may phenotypically affect the adipose tissue from these patients. We chose to include this as the control group as these samples not only collected in an identical manner from the same surgeons and processed identically, but also controls for potential non-secreting effects of pituitary tumor growths in the acromegaly subjects.**

In addition, the patients and controls are not age matched; while age has been shown to influence adipose tissue biology.

**The reviewer brings up an excellent point, as the previous analysis did not match the samples for age. To directly address this, we performed an additional supplementary analysis of the data wherein we separated the samples into subjects whom were over or above 40 years of age and repeated the analysis. This is described in the methods section as such:**

**To account for potential age-dependent changes in the subjects, we also did a supplementary analysis in which separated the patients into two groups, over 60 and under 60. We then added this age group as a covariate along with the disease state, also allowing for an interaction between the age group and the disease.**

**After this analysis we found that after controlling for age, we observed 75 genes that were significantly different between acromegaly and control patients. If we separated the analysis to look at each age group separately, we found 87 genes which were significantly different with acromegaly in the under 60 age group and 4 genes which were different in the over 60 age group. We have provided a new Supplementary Tables 5-7 describing these data, and their associated pathway analyses. This is now described in the results section as such:**

**To account for potential age-dependent changes in adipose tissue, we also performed a sub-analysis in which we stratified our subjects into two groups based on their age (over or under 60 years of age). Based on this sub-analysis, we observed that there were 87 genes that were significantly different after adjusting for age, 75 genes that were significantly different if we only examine subjects under 60 and 4 genes that were significantly different if we only examine subjects over 60. These gene-level data are presented in Supplementary Table 5, with pathway analyses presented in Supplementary Table 6 and transcription factor/miRNA analyses presented in Supplementary Table 7.**

**We have also carefully examined whether the genes and pathways discussed in this manuscript showed an age dependent effect. These effects are now noted where such an effect was significant in the results sections.**

Furthermore, it is not clear if the authors had into account the acromegaly onset, which is crucial to determine the time of high GH exposure.

Regarding the experimental approach, it seems that the authors did not further validate the transcriptomic analysis by qPCR or western-blot, which drastically lessen the reliability of the results.

It is neither clear why only 7 out of 9 patients were used for the study. In addition, the study lacks mechanistic studies and/or validations that confirms the direct action of GH on the analyzed genes.

**The missing two patients for whom we had phenotypic data but not RNAseq data were included in Figure 1 but not other analyses. This was described in the methods section:**

**These subjects corresponded to the patients described in Table 1, with the exception of subjects 29 and 31 (both acromegaly patients), which had clinical data but no RNAseq data.**

Other comments:

* Several of the results presented herein (glucose levels, insulin levels, lipolytic measurements) have been previously published by other. However, some of them did not reach statistical significance herein, reflecting the fact that the number of patients and/or replicates could be too low to draw consistent conclusions.
* It is surprising that the authors suggest adipose tissue relevant contribution to IGF plasma levels based on a mere correlation. Have the authors determined which is the real contribution of adipose tissue to IGF levels?
* The authors consistently refer to the effects of excess GH due to acromegaly, while acromegaly also curses with elevated IGF-I levels and therefore both elevated GH and IGF-I levels contribute to the final observed phenotype.