EDITORIAL REPORT  
  
Senior Editor  
Comments to the Author:  
The authors study gene expression in SC adipose tissue of Cushing's patients. The study is generally interesting, relevant and provides several novel findings. However, one concern is the age difference in the two cohorts, which should be accounted for statistically. Moreover, there are other limitations of the study, which should be appropriately discussed.  
  
Reviewers' Comments to Author:  
  
Reviewer: 1  
  
Comments to the Author  
Overall this is a study that identifies gene expression profiles in humans with Cushing's disease that are, more or less, endorsed in a mouse model of Cushing's. And provide a wealth of data that might prove to be useful when considering adipose tissue associated co-morbidities.  
The quality of the analysis seems to be of a good standard.  
The age of the human groups might add some underlying disparity but this I suspect this not a major issue. The mice were treated with dexamethasone, not the endogenous GC and so effects on genomic responses might be altered somewhat. A recent paper by Morgan et al, PNAS showed that the 11beta HSD1 enzyme is an important mediator of mouse Cushing's and Dex is not HSD1 metabolised. Might this alter the profiles in mouse compared to using corticosterone?  
  
At the end of my manuscript are a large number of pages of some sort of impenetrable table?? This needs either omitting or seriously re configuring.  
  
Figure 5a and 5b are a bit tricky to follow  and might need making more visually clear to the reader- such as being re drawn more as a cartoon?  
  
I found the discussion well balanced and did not over interpret the available data. It identified points of limitation (i.e. the age issue, the small numbers and potential confounders and overall I believe this is a good contribution to the literature in this field.  
  
Reviewer: 2  
  
Comments to the Author  
Major comments: This manuscript describes changes in adipose tissue resulting from chronic excess glucocorticoid exposure that may confirm suspected changes that occur in Cushings patients. While the mouse data strengthens the argument of the authors, the extremely small number of affected subjects has led to a number of conclusions that are not sufficiently supported by the data and statistical analysis.  
  
Suggested revisions:  
1.      The statistics section does not mention the use of a model that corrects for age in the Cushings and non Cushings groups. Has this been done? If so it should be addressed in this section and in the results. If not, a statistical model that corrects for age should be applied and reported.  
2.      For the gene expression studies, results need to be reworded to describe the results that were and were not statistically significant. While it is possible that a larger sample size would have yielded statistically significant results, conclusions about classes of genes should not be based on results that are not statistically significant.  
a.      Be careful with the use of “trend” where there is a tendency toward a difference in the absence of statistical significance as trend means something else.  
b.      Lines 267-69 and figure 4A, are these genes significantly increased? If so, please indicate on graph. If not, please reword the text accordingly.  
c.      Lines 270-72 and figure 4B, as above.  
d.      Line 286, and 291-94, same.  
3.      Consider representing the gene expression data as a table that includes the p values. The graphs are cumbersome and don’t add to the manuscript.  
4.      Lines 337-39, 340 and figure 7A; this graph should be removed and text rewritten. There are no clear differences, statistically or otherwise.  
5.      Figure 7B should be provided as supplemental data; same for 7C, or include data as part of gene expression table that includes p values.  
6.      Likewise, figure 8A can be included in tabular form or expressed textually by describing the fold changes for obese and non-obese groups. Figure 8B should also be eliminated or included as supplemental data.  
7.      The discussion lacks depth in its explanation of gene expression profile changes (i.e. lines 386-89),  
a.      the statistical analysis and models used should be discussed here to explain how the limitation of small number of subjects was overcome, at least in part.  
b.      Lines 402-06 should be rewritten to reflect which differences were statistically significant and discussed in greater depth.  
  
8.      In the methods section, a description of how subcutaneous fat mass was assessed should be included. It appears that inguinal fat pads were dissected and weighed but this should be clearly stated.