

Basic Reporting:

The paper was clear and concise, and it fits to the basic reporting criteria. Literature was well referenced & relevant with the context. You might want to talk more about mega-analysis and why you chose this method instead of other methods in the literature. Figures are relevant but, if you can, you should increase the resolution on Figure 2 for the actual publication.

In line 159, you mentioned “About 67.04% of the obesity-genes (358 out of 534 genes) have not been reported to have an association with TC. Thus, we tested the expression changes of these 358 genes in the case of TC.” You might want to talk more in detail about how you obtained these numbers (I am assuming you used Pathway Studio.)

Experimental Design:

I have found no problems with your study design, but I have some concerns about background correction for the different datasets you used. Did you take any measures to nullify the effects of different studies introducing noise to your findings? You might want to talk about this issue in your discussions to make a stronger point and prove the validity of your findings.

Suggestions for improving the writing:

34: Previous studies indicate that obesity is an important contributor to the development of

36: You might want to change development with proceeding

46: Use “were identified” instead of have been identified?

48: Use control or modulation instead of regulation?

50: Consider using provision, management or control instead of regulation

62 However, inconsistent results were represented, which could be due to the unbalanced sex in the TC samples

89: you might consider using “has proven to be” instead of has been shown to be

97: Change were with “was”

104: Change available with accessible

122: Proposing to change “implicated” with “associated”

154: “For detailed information ‘on’ these genes” would be better to use

167: Proposing to use provided instead of presented

186: There is a dot “.” before while that needs to be changed. Use a comma and uncapitalize while?

209,210: You don't need "with each other" at the end of the sentence.

216-219 "Towards this purpose, we first used the knowledge-based algorithms to analyze disease-gene relation data and reveal 176 obesity-regulated genes. Identified genes were also related to TC and utilized to build a common background at the genetic level for the etiology of both obesity and TC." **If you liked the sentence, you could use it with modifications you see fit**

236: "stimulating" is used plenty of times. You can use "promoting" before insulin-like growth factor

238: Use "obese" instead of "obesity"?

253, 254: Use "positively or negatively" instead of "in a positive or negative way"?

258: You can use robust instead of strong

264: I don't think you need to mention the lack of space. Just say that due to your criteria enforcement, you opt to talk only about 5 genes which passed introduced thresholds and other genes are also worth looking into.

Extra Suggestions:

Using the 5 genes you identified, I was able to get some interesting findings in Hetionets. <https://neo4j.het.io/browser/>

If you create a new disease and connect them with the 5 genes you have found, you can query the database in such a way that why these genes are more important than we might initially think. The query I used looks for the relationship of identified genes with other genes. Then, it tries to associate these genes with biological processes. The results are below:

go_id	go_name	PC	DWPC	n
"GO:0060397"	"JAK-STAT cascade involved in growth hormone signaling pathway"	14	0.0006984799232056969	24
"GO:0035335"	"peptidyl-tyrosine dephosphorylation"	16	0.0006737656249958966	99
"GO:0060396"	"growth hormone receptor signaling pathway"	15	0.0006540141788364426	27
"GO:0071378"	"cellular response to growth hormone stimulus"	15	0.0006398977800322438	28
"GO:0046326"	"positive regulation of glucose import"	6	0.0006181606039400545	37

go_id	go_name	PC	DWPC	n
"GO:0010828"	"positive regulation of glucose transport"	6	0.0005648606021185907	43
"GO:0060416"	"response to growth hormone"	15	0.0005245255623867113	39
"GO:0046324"	"regulation of glucose import"	7	0.00048137960347858046	60
"GO:0006470"	"protein dephosphorylation"	17	0.00046434833045504815	18
"GO:0030512"	"negative regulation of transforming growth factor beta receptor signaling pathway"	6	0.00042324590546277636	77
"GO:1903845"	"negative regulation of cellular response to transforming growth factor beta stimulus"	6	0.00042324590546277636	77
"GO:0097696"	"STAT cascade"	14	0.0004156767741625712	57
"GO:0007259"	"JAK-STAT cascade"	14	0.0004156767741625712	57
"GO:0010757"	"negative regulation of plasminogen activation"	2	0.0003806146302769252	5
"GO:0016311"	"dephosphorylation"	17	0.00036446771498809937	27
"GO:0010827"	"regulation of glucose transport"	7	0.00035012113851283787	10
"GO:0017015"	"regulation of transforming growth factor beta receptor signaling pathway"	7	0.0003473203535193284	11
"GO:1903844"	"regulation of cellular response to transforming growth factor beta stimulus"	7	0.0003473203535193284	11
"GO:0090101"	"negative regulation of transmembrane receptor protein serine/threonine kinase signaling pathway"	6	0.00033271202399419686	11

go_id	go_name	PC	DWPC	n
"GO:0090288"	"negative regulation of cellular response to growth factor stimulus"	8	0.0003096965436520812	13
"GO:0010755"	"regulation of plasminogen activation"	2	0.0002511120078031516	10
"GO:0051918"	"negative regulation of fibrinolysis"	2	0.0002511120078031516	10
"GO:0090287"	"regulation of cellular response to growth factor stimulus"	10	0.0002329709773515661	24
"GO:0001503"	"ossification"	3	0.0002280567905096033	25
"GO:0090092"	"regulation of transmembrane receptor protein serine/threonine kinase signaling pathway"	7	0.00022790510892379073	22

From what I understand , these genes and the genes they interact with have significant relationships with response to growth hormone, glucose transport and import, negative regulation of cellular response to transforming growth factor beta stimulus and JAK-STAT cascade involved in growth hormone signaling pathway. This ties the results of the paper with Insulin, TC and Obesity in a great way. If you want, I can make the code and instructions available for navigating through the Hetio database. I hope that this would contribute to your Discussion section if you choose to review it before submission.