Author’s response to reviews

Title: Disentangling the Genetics of Sarcopenia: prioritization of NUDT3 and KLF5 as genes for lean mass & HLA-DQB1-AS1 for hand grip strength with the associated enhancing SNPs & a Scoring system

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GTC-D-19-00431R2

Disentangling the Genetics of Sarcopenia: prioritization of NUDT3 and KLF5 as genes for lean mass and HLA-DQB1-AS1 for hand grip strength based on associated SNPs

Abhishek N. Singh, M.Tech, MBA, PhD candidate; Bili Gasman

BMC Medical Genetics

Dear Mr Singh,

Your manuscript "Disentangling the Genetics of Sarcopenia: prioritization of NUDT3 and KLF5 as genes for lean mass and HLA-DQB1-AS1 for hand grip strength based on associated SNPs" (MGTC-D-19-00431R2) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Medical Genetics, once you have carried out some essential revisions suggested by our reviewers.

Their reports, together with any other comments, are below. Please also take a moment to check our website at https://www.editorialmanager.com/mgtc/ for any additional comments that were saved as attachments. Please note that as BMC Medical Genetics has a policy of open peer review, you will be able to see the names of the reviewers.

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We request that a point-by-point response letter accompanies your revised manuscript. This letter must provide a detailed response to each reviewer/editorial point raised, describing what amendments have been made to the manuscript text and where these can be found (e.g. Methods section, line 12, page 5). If you disagree with any comments raised, please provide a detailed rebuttal to help explain and justify your decision.

Please also ensure that your revised manuscript conforms to the journal style, which can be found at the Submission Guidelines on the journal homepage.

A decision will be made once we have received your revised manuscript, which we expect by 24 Feb 2020.

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We look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Kamlesh Guleria

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Technical Comments:

1. Modify the titles of tables and figure. Title should be brief and self-explanatory.

RESPONSE: Thank for the comment, table and figure names were modified to be more comprehensible. See pages 6-13,

examples of changes:

Page 6:
"Figure 1. Gene expression based on SMR of GTEx eQTLs and whole-body lean mass GWAS."

"Figure 2: Gene expression based on SMR of GTEx eQTLs and appendicular lean mass GWAS"

Page 8:
"Table 7: SMR of GTEx skeletal muscle eQTLs and handgrip GWAS."
"Table 8: GTEx Handgrip GWAS data with eQTL aggregated SMR."

Page 11:
" Figure 5. KLF5 expression in chromosome 13 (psoas muscle)."

Page 12:
" Figure 6. NUDT3 expression in chromosome 6 (bladder muscle)."

2. Table 1 is not cited in the text. Italicize the gene symbols in table also.

RESPONSE: Thanks, fixed the table issue and italicized the gene symbols

3. Modify column of Table as
Probe ID    Chromosome    Gene    Base pair of probe    Associated SNP

RESPONSE: Thank you for the comment, tables fixed

4. Delete the agenda from each table and figures.

RESPONSE: Done, added figure explanation within the figure itself.

5. The discussion part (specially last 2 paragraphs) “The above information emphasizes that these genes are not directly related to muscle health, yet they …………of the results presented in this study results can serve as a test to whether our approach to gene prioritization can resolve this problem” need modification. The method used for prioritization should be explained in method section. In discussion, discuss your findings only.

RESPONSE: Thanks for the comment. The scoring system wasn’t utilized in this study. It is a method of further prioritizing the study's data for wet lab validation, thus it fits into the discussion section rather than the methods, preliminary results of wet lab validation were
accepted as a poster presentation in ICFSR 2020 and will be published in the proceedings in the Journal of Frailty & Aging (ISSN: 2273-4309). As explained in the discussion section (page 2: "Functional validation is a slow and costly process…. an effect on muscle health"), wet lab verification takes time and is a costly process, so this scoring system allows us to narrow down the genes that are likely to be validated in wet lab as related to muscle health. Discussion of further investigation and verification of the data analyzed in this study is as well as discussion other aspects of data analysis (the scoring system) are crucial since without further study and validation the results remain purely theoretical.

6. Conclusion should be brief. It is too lengthy and speculative.

RESPONSE: Thank you, fixed the conclusion section, making it less speculative and shorter.

Overall the conclusion section was shortened from 196 words to 149 words.

Page 4:

conclusion

The current work focused primarily on the combined bioinformatic approaches using GWASs and eQTLs for &lt;summary-data based Mendelian randomization&gt; (SMR). The results of exclusivity of the tissues of interest were further classified for their importance based on Venn diagrams and their corresponding TAD plots to look for the TAD boundaries where the associated regulating SNPs could be localized. NUDT3 and KLF5 for lean mass and HLA-DQB1-AS1 for hand grip strength and their associated SNPs (rs464553, rs1028883 and rs3129753) had the highest priority as candidate targets for new or repositioned drugs. (changed to "for further study.")

One limitation of this study is that the eQTL analysis was not done on trans-association SNPs. Another is the limited knowledge on TAD function. &lt;In order to further assess, the results functional validation of the results is required.&gt;

We propose wet lab (changed to "functional") validation to &lt;ascertain the association of enhancement of a gene for patients with a SNP genotype that was associated positively with gene enrichment in the current study, thus&gt; either proving or rebutting (changed to: "either prove or rebut.") the effect of prioritized genes on muscle tissue (changed to "health"). We also proposed further steps that can be taken to further prioritize candidate genes as targets for new drugs or for existing drug repurposing. (changed to: ", thus widening the scope of knowledge on the genetic origins of sarcopenia.")

Reviewer reports:

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If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.