Reviewer’s report

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

Version: 1 Date: 24 Oct 2019

Reviewer: Amrik Sahota

Reviewer's report:

A. Major comments

The manuscript uses bioinformatics approaches on published GWAS data (for lean mass and hand grip strength) and eQTL data (based on GTEx and other sources, collectively referred to as TWAS) to prioritize genes that may be associated with sarcopenia, a condition associated with degenerative loss of muscle tissue. Using these approaches, the author identified NUDT3 and KLF5 as candidate genes for lean mass and HLADQB1-AS1 as a candidate gene for hand grip strength.

As the author indicates, quantitative real-time PCR studies in muscle tissue are required to confirm these findings, but a brief description of the potential role of these genes in the respective phenotypes should be included in the manuscript. HLADQB1-AS1, for example, encodes a cell surface receptor involved in the immune system and KLF5 encodes a transcription factor. How can these genes be potentially linked to hand grip strength and lean mass, respectively?

The author also states that lean mass and grip strength need to be assessed independently as these two factors vary with age. There was no mention in the manuscript on age as a variable in the eQTL studies.

The author mentions two muscle types: psoas (skeletal) and bladder (smooth). Did the eQTL data differentiate between these muscle types?

For appeal to a wider audience, the manuscript could benefit from the inclusion of a brief description of the bioinformatics tools used for analysis.

B. Minor comments:

1. Abstract

   a. Abstract without author information (which presumably is the original abstract) does not match the abstract with author information (which presumably is the revised abstract). I cite two examples. TWAS is spelled out
in the revised abstract, but not in the original one. TADs are mentioned in the original abstract but not in the revised one.

b. Line 28: Remove s from GWASs. Same for other places in the manuscript.

c. Line 34: Place gene names (NUDT3 and KLF5) in italics. Same for other places in the manuscript.

2. Background section

a. Most abbreviations are described when first used in the text. GTEx should be described as well.

3. Figures

a. Figure 11 is out of place. It appears between Figures 2 and 3.

b. For many of the figures, figure headings appear to be out of alignment and the allele frequency column appears to be missing in a few cases.

c. It would be useful to give a brief description of the column heading in the first figure.

d. Most of the figures are table and should be labeled as such.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
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I recommend additional statistical review
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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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