



MEMORANDUM

To: Dr. Zilin Li

From: JHS Publications & Presentations Committee

Date: September 25, 2023

RE: Manuscript Review (#1744: Whole Genome association testing in 333,100 individuals across three Biobanks identifies rare non-coding single variant and genomic aggregate associations with height)

The JHS Publications and Presentations Committee reviewed your manuscript and it has been **accepted with comments**. Please see the committee's comments below.

Manuscripts with National Institutes of Health (NIH) author/co-authors must be reviewed by the National Heart, Lung, and Blood Institute (NHLBI). In this case, the lead author must send the manuscript and the P&P approval letter via email to NHLBI nhlbi_ebpdocs@nhlbi.nih.gov and copy the Project Officer, Dr. Sharon Smith, smithsh1@mail.nih.gov before submission to a journal for publication.

The following **acknowledgement** and **disclaimer** must be included in your submitted manuscript:

JHS acknowledgement- The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS.

JHS disclaimer- The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

You must **adhere** to the following **NIH Public Access Policy**. NIH-funded investigators shall submit to the NIH National Library of Medicine's (NLM) PubMed Central (PMC) an electronic version of the author's final manuscript, upon acceptance for publication, resulting from research supported in whole or in part with direct costs from NIH. NIH defines the author's final manuscript as the final version accepted for journal publication, and includes all modifications from the publishing peer review process. The PMC archive will permanently preserve these manuscripts for use by the public, health care providers,

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educators, scientists, and NIH.

Thank you for collaborating with the JHS.

Comments

Please Note: The authors have responded to the following committee comments.

1. Unlike All of Us and UK Biobank, TOPMed is not a cohort or a 'study', This should be clarified in the wording (e.g. Abstract).
2. It is not clear why JHS is included, as the only analyses including those with African ancestry appear to be conducted on those in UK and then All of US.
3. You should consider mentioning in the Discussion that the analyses on those who did not have European ancestry had a smaller N, and therefore, could have been underpowered (depending on effect sizes, allele frequencies etc, but in general this can't be ruled out...). This would ensure there isn't an unconscious bias to focus on the importance of the results in European ancestry individuals and/or lend to the conclusion that height is less heritable in those without a European ancestry. The authors addressed the critiques. The outcome measures have been simplified. Plans for analyses are clear. There are no new major comments.
4. Not so much that JHS is misrepresented, but it is not clear why JHS is included. The analysis was done in three stages. From the manuscript:
 - a. We performed discovery association analyses using whole-genome sequencing data on 200,003 individuals from the UKB, a population cohort from the United Kingdom
 - i. No JHS as UKB only
 - b. 2A: We then replicated our results in 87,652 and 45,445 individuals with inferred European ancestry with WGS data in All of Us and TOPMed respectively"
 - i. No JHS as European ancestry only
 - c. "as well as 20,548 and 13,683 individuals of African and Hispanic ancestry from All of Us."
 - i. No JHS as All of Us Only
5. It is unclear why JHS is included as all TOPMed analyses seem to be on those with genetically inferred European ancestry.