November 4, 2024

Dear Editors,

We are pleased to submit our manuscript entitled “Transcripts with high distal heritability mediate genetic effects on complex metabolic traits” as a research article in *Nature Communications*.

There is an emerging and controversial theoretical hypothesis in population genetics that distal gene regulation may account for the bulk of heritable trait variation (Boyle, et al., *Cell*, 2017; Liu, et al., *Cell*, 2019), but there have been no experimental tests of these ideas because of the challenges dissociating local and distal effects with sufficient statistical power. In this study, we leveraged unique mouse genetic diversity resources to address this question experimentally for the first time. Using diet-induced obesity and metabolic disease as archetypal examples of complex traits, we found that most trait-relevant gene expression differences are distally inherited rather than mediated through local eQTL. This finding resulted from two large, genetically diverse mouse populations for discovery and validation, transcriptomes from multiple tissues of each mouse, and a novel high-dimensional mediation analysis to infer how genetic effects are mediated through gene expression to affect clinically relevant traits. This study design is essentially impossible in human subjects and therefore provided a unique opportunity to test foundational questions of genetic architecture.

In a comprehensive series of analyses powered by our novel high-dimensional mediation framework, we demonstrated that distal regulation of gene expression is the primary driver of trait variation. Our key results are that distally heritable transcriptomic signatures translated to a second, independent mouse population as well as to four human studies. The latter result constitutes an unprecedented success in translating mouse genetics to human disease and offers a paradigmatic shift in the clinical interpretation of model organism results.

Our findings have profound implications for the interpretation of genome-wide association studies (GWAS) and translation of results from model organisms to humans. Current interpretations of GWAS often presume that genetic variation influences complex traits through local regulation of gene expression; however, efforts to identify local eQTL that influence disease have largely failed, and statistical methods that infer clinical states from local eQTL do not translate across human populations. Our findings demonstrate that this failure follows from a deep fact about genetic architecture.

We believe that this manuscript will be of broad interest to scientists working in translational genetics. The manuscript includes main text, eight figures, thirteen supplementary figures, and two supplementary files. We also provide free access to an expansive mouse data set intended to serve as a community standard for complex trait analyses linking genetics and gene expression.

No author has any financial, personal, or professional interests that could be construed to have influenced the paper. Thank you for your consideration of this manuscript.

Sincerely on behalf of all authors,



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