October 16, 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 Genetics*.

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.

Our key result is the first experimental validation of emerging ideas about the importance of distal gene regulation in complex trait genetics and has profound implications for the interpretation of genome-wide association studies. Current interpretations of GWAS often presume that genetic variation influences complex traits through local regulation of gene expression; however, recent studies in *Nature Genetics* have suggested the alternative possibility that distal effects may be more relevant (Yao et al. 2020; Vosa et al. 2021; Mostavi et al., 2023). These findings are consistent with the recently proposed omnigenic model of complex traits, which posits that diffuse distal effects converge on core, trait-driving genes that are themselves buffered against genetic variation (Boyle, et al., *Cell*, 2017; Liu, et al., *Cell*, 2019).

Because human genetic studies are inherently limited when combining genomes, transcriptomes, and clinical traits in the same study, we used an artificial population of genetically diverse, outbred mice to rigorously test the importance of local and distal effects on the transcriptomes in multiple relevant tissues. 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 resulting model was predictive of outcomes in a second mouse population and in four human studies. The latter constitutes an unprecedented success in translating mouse genetics to human disease.

We believe that this manuscript will be of broad interest to geneticists. 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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