October 28, 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 *Cell*.

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 study provides the first experimental validation of the omnigenic model first proposed in *Cell* (Boyle, et al. 2017; Liu, et al. 2019)*.* This model posits that diffuse distal effects converge on core trait-driving genes that are themselves buffered against genetic variation. Although recent studies in human populations in have suggested that distal effects may be more relevant than local effects on gene expression (Yao et al. 2020; Vosa et al. 2021; Mostavi et al., 2023), our study provides clear experimental evidence that distal gene regulation is more relevant to complex traits than local regulation.

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. The manuscript includes main text, seven figures, fourteen supplementary figures, and a supplementary file. 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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