Complex metabolic traits are mediated by genes with distal heritability

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The preponderance of non-coding genetic associations in human disease suggests that alterations in gene expression may commonly influence trait outcomes. Abundant gene expression quantitative trait loci (eQTL) provide further evidence that genetics often express through transcriptional regulation. We used Diversity Outbred and Collaborative Cross mice to explore and quantify this mechanism. We integrated multiple physiological measures of metabolic health with multi-tissue gene expression to determine how eQTL may mediate genetic influence on trait outcomes in mice. Using high-dimensional mediation analysis, we found that traits were primarily mediated by the expression of genes with high distal heritability, instead of genes with local eQTL. This suggests that broader network effects are more relevant to physiological outcomes than local genetic effects on gene expression. We furthermore found that trait-mediating genes are strongly enriched in common functions and likely to be previously associated with metabolic outcomes. We validated these results using F1 progeny of selected Collaborative Cross strains and demonstrated translation to human metabolic disorders. These findings highlight the utility of mouse populations that exploit and manipulate standing genetic diversity to dissect molecular intermediaries of health and disease.