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LETTER

Comment on "Multi-Omics Association Analysis of Mitochondrial Genes in Hypertrophic Scars: Application of Mendelian Randomization" [Letter]

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Dear editor

We read with interest the multi-omics Mendelian randomization (MR) analysis of mitochondrial genes and hypertrophic scars (HS) by Gong et al, which identifies HTATIP2 and PDK1 as putative causal genes.[1] The study is ambitious and innovative, yet several methodological and interpretative issues may temper the strength of the causal claims.

First, all molecular instruments are derived from blood mQTL/eQTL/pQTL datasets, whereas HS is primarily a fibroblast- and dermis-dominated phenotype. Large consortia such as GTEx have shown that eQTL effects are frequently tissue- and even cell-type–specific, with many regulatory variants active in only a subset of tissues.[2] Multi-omics QTL resources likewise emphasize strong tissue/cell specificity.[3] The authors should more clearly acknowledge that their instruments may capture systemic immune or hematologic pathways rather than skin- or fibroblast-specific regulation, and ideally explore whether key signals replicate in skin/fibroblast QTL datasets.

Second, the MR analyses use cis-SNPs pruned at r^2=0.3 and then apply standard IVW/Egger models that assume independent instruments. Correlated variants can inflate precision, distort Cochran's Q, and compromise pleiotropy tests. Recent MR methods explicitly account for LD and complex correlated pleiotropy (eg, MR-Corr2, MR-CUE) and are recommended in exactly this setting.[4] Re-analysis with LD-aware MR would make the causal estimates more reliable.

Third, while extensive sensitivity analyses are presented, residual horizontal pleiotropy is a major concern for mitochondrial genes that influence broad metabolic and inflammatory pathways. Contemporary guidance stresses that Egger, weighted median/mode and MR-PRESSO have limited power when instrument numbers are small or highly correlated, and that MR results should be interpreted as supportive rather than definitive evidence.[5]

Fourth, the logic of multi-omics integration deserves greater caution. Colocalization identifies robust H4 support only for selected mQTL and eQTL signals, and no pQTL–HS colocalization is detected, yet HTATIP2 and PDK1 are promoted as tier-1 genes with convergent evidence. Current best practice recommends that MR findings be combined with consistent colocalization at each layer to reduce the risk that methylation, expression and protein signals arise from distinct causal variants in LD.[6] Recent methodological work on multi-omics MR also highlights the value of formal combination tests and mediation-oriented frameworks rather than heuristic tiering.[7]

Finally, the biological interpretation of HTATIP2 and PDK1 could be further nuanced. Both genes are deeply embedded in generic angiogenic, apoptotic and metabolic networks, and prior studies suggest context-dependent, sometimes opposing roles across tissues and disease states.[8] Without integrating scar-specific cell states (myofibroblast activation, mechanotransduction, immune infiltration) and considering alternative pathways by which these genes may influence HS risk, the conclusion that they are ready therapeutic targets may be premature.

Overall, this study identified 21 mitochondrial genes with therapeutic potential, which may enhance our understanding of the pathophysiology of HS. Meanwhile, addressing these issues, particularly the tissue specificity of the

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instrument, LD perception of MR, stricter use of co localization, and more cautious biological discussions, will greatly enhance the manuscript and its translation significance.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

Xiang Deng: Conceptualization, Writing-original draft. Zihan Zhao: Conceptualization, Writing-original draft. Zhongsong Zhang: Conceptualization, Writing-original draft.

All authors approved the final version accepted for publication; agreed on the journal to which this communication was submitted; and agreed to take responsibility and be accountable for the contents of this communication.

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