From Correlation to Causation: How Omics Technologies Illuminate the Role of INHBC in 2 Cardiometabolic Disease

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The integration of omics technologies such as genomics, proteomics, and metabolomics into clinical research has enabled discoveries of complex biological mechanisms underlying disease. In this commentary, we examine recently published data outlining the use of multi-omics to investigate the liver-derived protein inhibin-βC (INHBC) and its role in cardiometabolic health. Through bidirectional Mendelian Randomization and phenome-wide analysis, INHBC was identified as both a driver and consequence of metabolic dysfunction, including obesity, dyslipidemia, and inflammation.This review discusses the contribution of INHBC to coronary artery disease risk by altering lipid levels which was also associated with renal and liver traits. Further, how INHBC exerts is pathological effects- through its transformation into activin C and signaling via the ALK7 receptor which suppresses fat breakdown in adipose tissue- will be discussed. These findings position INHBC as a potential biomarker with translational therapeutic relevance in complex disease pathways, like cardiometabolic disease.

Introduction

In the post-genomic era, the convergence of omics technologies (i.e., genomics, proteomics, transcriptomics, and metabolomics) has revolutionized biomedical research.[1] Researchers are no longer limited to identifying associations between biomarkers and disease traits; instead, they can interrogate the causal architecture of complex diseases to identify therapeutic targets and develop system-level models of human physiology.

This commentary critically analyzes work by Loh et al., which exemplifies a paradigm shift in the role of inhibin-βC (INHBC), a member of the transforming growth factor (TGF)-β superfamily, in cardiometabolic disease.[2] INHBC is the precursor to the homodimer activin C, a protein typically viewed as a minor regulator of activin bioactivity due to its limited mRNA expression and lack of abnormality in INHBC-null mice.[3] Previous proteome-wide Mendelian randomization studies identified an association between INHBC and a greater progression of CKD.[4,5,6] However, there is no clear consensus on whether INHBC actively contributes to disease progression or rather reflects metabolic stress. This ambiguity is striking given the broader interest in the activin family, whose members (including activin A and B) are known to modulate cell growth, lipid metabolism, and inflammation through SMAD signalling pathways.[7]

A recent study used integrative omics technologies to test whether INHBC acts as a causal driver of metabolic dysfunction and cardiovascular disease risk or whether it simply reflects these conditions. Their study employed a powerful combination of genome-wide association studies (GWAS), protein quantitative trait loci (pQTL) mapping (where genetic variants near a gene influence its protein expression), bidirectional Mendelian Randomization (MR; a genetic method that uses inherited variants to infer the direction of causal relationships), phenome-wide association studies (PheWAS; screening a wide range of health traits for associations with a single genetic exposure), and functional assays in human adipocytes.[2] These methods provided a comprehensive view of INHBC's role in lipid metabolism, inflammation, and cardiovascular risk, clarifying both the directionality and underlying biological mechanisms.

The objective of this commentary is to critically evaluate how Loh et al.'s integrative omics approach determined the causal role of INHBC in metabolic disease, to situate their findings within the broader context of omics-driven discovery, and to highlight key challenges that arise when translating these insights into clinical and therapeutic applications.

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Omics at the Core: Multi-Layered Insight into Causality
Central to the study is the use of bidirectional MR, an approach that mimics a natural randomized trial by using inherited genetic variants as proxies for modifiable exposures.[8] Because genetic variants are randomly allocated at conception and remain fixed throughout life, MR minimizes the confounding and reverse causation seen in observational studies. Bidirectional MR strengthens causal inference by testing whether the relationship operates in both directions: from the exposure (INHBC) to disease traits and from disease traits back to the exposure.[6] In this study, the dual design revealed a self-reinforcing cycle: elevated INHBC levels causally increased low-density lipoprotein (LDL) cholesterol, triglycerides, inflammation, and coronary artery disease (CAD) risk, while central adiposity, hypertriglyceridemia, and inflammation themselves raised circulating INHBC.[2] These reciprocal effects underscore the power of MR to establish likely directions of causality.[8] Nonetheless, MR relies on assumptions such as the absence of pleiotropy which, while addressed through sensitivity analyses, can never be fully excluded.[8]

What makes this study particularly compelling is the depth of omics integration. The authors used cis-pQTL instruments from over 35 000 Icelandic participants to perform MR against outcomes from large European-ancestry GWAS cohorts.[2] This allowed for high-resolution mapping of INHBC's effects on lipid traits, systemic inflammation, and anthropometric indices, such as BMI-adjusted waist-to-hip ratio (WHRadjBMI). The reverse MR used similarly robust instruments to establish that metabolic traits also drive INHBC levels, reinforcing a feedback loop.[2]

Mechanisms, Mediation, and Metabolic Dysfunction

The study further incorporates multivariable MR and mediation analysis, advanced tools in the omics toolkit, to determine how much of the observed effects were direct versus mediated through intermediate traits. For example, 26% ($\beta \pm SE; 0.088 \pm 0.0034$) and 23% ($\beta \pm SE; 0.122 \pm 0.025$) of BMI's impact on INHBC was mediated by triglycerides and CRP, respectively.[2] Similarly, 35% ($\beta \pm SE; 0.062 \pm 0.031$) of the effect of WHRadjBMI was mediated through triglycerides.[2] These nuanced insights would not be possible without multi-layered omics data and modern causal inference methods. Still, mediation analysis can be sensitive to measurement error and unmeasured confounding variables, and these models depend heavily on the assumption of no residual confounding between mediators and outcomes.[7]

In terms of downstream outcomes, INHBC was found to modestly increase the risk of CAD and non-alcoholic fatty liver disease (NAFLD).[2] However, no effect was observed on type 2 diabetes (T2D).[2] Further mediation analysis revealed that 40% ($\beta \pm SE; 0.016 \pm 0.008$) of INHBC's effect on CAD was mediated through lipid traits, particularly high-density lipoprotein (HDL) cholesterol, highlighting the power of omics to pinpoint mechanistic intermediaries.[2]

PheWAS and the Broad Reach of Omics

Beyond MR, the study's PheWAS explored INHBC's associations across 367 traits, offering a panoramic view of its systemic impact. Significant associations emerged not only in lipid metabolism and statin use, but also in renal dysfunction (e.g., lower estimated glomerular filtration rate, higher serum urea, and creatinine), hyperuricemia, and calcium regulation.[2] Although some of these effect sizes were modest, their consistent directionality and colocalization with causal variants strengthen the argument for INHBC's involvement in diverse physiological systems.[2]

This PheWAS approach reflects the true power of omics: to take a candidate protein and rapidly map its influence across a wide array of biological outcomes, generating testable hypotheses that extend beyond traditional disease categories. For example, the study suggests that elevated INHBC may contribute to kidney stress, raising questions about its role in fibrosis and chronic kidney disease, areas of active investigation in related research.[4,5,6] Still, the PheWAS approach involves multiple testing which, even with stringent statistical corrections, raises the possibility of false-positive associations and highlights the need for further validation in independent cohorts.

Experimental Validation and Expanded Functional Insight: Connecting Omics to Function

One of the most compelling aspects of this study is how it bridges large-scale omics data with cellular biology. Using dedifferentiated human adipocytes from both abdominal and gluteal depots, the authors tested whether the omics-identified protein product of INHBC, recombinant activin C, could directly modulate metabolic

processes. Their experiments showed that activin C activates the ALK7 receptor, triggering SMAD2/3 phosphorylation and suppressing adrenaline-stimulated lipolysis.[2] These findings strongly support the omics predictions; however, translation to in vivo systems, where tissue-specific expression and physiology come into play, will be essential.

Notably, the signalling response to activin C was initially weak due to low baseline ALK7 expression, mirroring real-world variation in tissue responsiveness.[2] However, when ALK7 was induced using a doxycycline-inducible vector, activin C robustly triggered SMAD2/3 signaling.2 These results confirmed ALK7 as the receptor mediating INHBC's effects and validated the predicted liver–adipose signalling axis.

The ALK7-SMAD2/3 pathway is known to regulate metabolic, inflammatory, and fibrotic responses.[10] Its demonstration here adds functional weight to the causal claims of MR and pQTL analysis and raises questions about INHBC's possible role in kidney disease and fibrosis. Future studies using tissue-specific transcriptomics and single-cell proteomics will be crucial to map INHBC's systemic impact. Here, we highlighted the power of omics-driven research moving from high-dimensional data to specific, testable molecular hypotheses. It exemplifies how genomics and molecular biology can work together to unravel complex disease mechanisms.[2]

Omics Implications: Beyond This Study

The value of omics in this study lies not only in its methods but in its implications. First, it establishes INHBC as a hepatokine with pleiotropic effects across organ systems. Second, it demonstrates how omics frameworks, ranging from GWAS to pQTLs to MR to PheWAS, can be utilized to deconstruct both disease etiology and therapeutic opportunities. Third, it opens the door to pharmacogenomic precision: variants like rs2229357 (INHBC missense) and rs3741414 (3'UTR) were found to colocalize with CAD and lipid traits, providing targets for personalized intervention.[2] However, the modest effect sizes observed in many of these associations, while robust in directionality, suggest that INHBC is likely only one component in the multifaceted landscape of metabolic disease. For therapeutic applications, these small effect sizes indicate that INHBC-targeted interventions would likely have incremental impacts when used alone and may be best evaluated in the context of combination therapies or personalized risk profiles.

Perhaps most importantly, this paper suggests that omics approaches have the potential to shift the medical model from reactive to predictive. INHBC, which has been relatively underexplored, is now positioned as both a biomarker and a possible contributor to metabolic dysfunction, supported by genetic and functional data. In a clinical future that increasingly relies on proteomic and genomic profiling, such molecules could help inform more precise prevention strategies.[2]

Limitations and Caution in Omics Interpretation

Despite its strengths, the study underscores key limitations of omics interpretation. The reliance on European-ancestry datasets limits generalizability to global populations, underscoring the need for validation in more diverse genetic backgrounds. Another layer of complexity arises from the inherent challenges in integrating multi-omics data. Differences in sample sizes, data types, and measurement platforms can introduce heterogeneity and bias, requiring careful harmonization and validation to ensure that conclusions are robust and reproducible.[11] Harmonization issues across omics layers, such as aligning cis-pQTL data with GWAS/PheWAS results, are particularly critical when moving from discovery to translational applications.[11] This emphasizes the importance of standardized data collection, transparent data management, and rigorous cross-validation to minimize confounding factors.

Biological causation also depends on functional validation; although the study addresses this through in vitro adipocyte studies, several questions remain. Notably, while lipid traits mediated 40% of the increased CAD risk with upregulated INHBC, the remaining 60% remains unexplained, raising questions about other potential mediators, such as inflammation, endothelial dysfunction, or oxidative stress. Future research should incorporate dynamic and tissue-specific omics layers, such as metabolomics, to capture how INHBC's expression and function shifts with metabolic states and to better understand its complex roles in disease progression.[11]

Finally, while the study positions INHBC as a promising clinical biomarker and therapeutic target, several challenges warrant caution. As a hepatokine and member of the TGF-β superfamily, INHBC's circulating levels and downstream effects are likely influenced by broader metabolic and inflammatory processes.[7] This context-dependent regulation could limit its specificity as a clinical marker and raises questions about reproducibility across different populations and disease contexts. These considerations underscore the importance of integrating INHBC into multi-marker risk models or broader precision medicine frameworks rather than relying on it in isolation.

Moreover, translating these omics insights into clinical practice requires not only addressing statistical challenges but also grappling with ethical and logistical barriers, including patient data privacy and equitable access to omics-informed care. These considerations emphasize the need for both technical rigour and broader ethical frameworks to realize the promise of omics in translational precision medicine.

Conclusion

A Blueprint for Omics-Driven Discovery

Loh et al.'s study provides a compelling example of how omics technologies can illuminate disease biology in unprecedented detail. By integrating genomic, proteomic, and functional data, the authors move beyond correlation to suggest causality, uncover potential therapeutic pathways, and highlight promising avenues for clinical translation. The study's implications extend beyond INHBC itself, offering a methodological roadmap for future efforts to unravel complex biological networks and gain a deeper understanding of disease mechanisms.

Nevertheless, as this commentary emphasizes, caution remains warranted. Translating omics findings into clinical practice requires addressing modest effect sizes, harmonizing data across platforms, and validating functional relevance in diverse populations. INHBC, while implicated as both a biomarker and possible contributor to metabolic dysfunction, illustrates the broader challenges and promise of omics-informed discovery. In an era where medicine is gradually shifting from generalized treatment to more targeted interventions, omics technologies are poised to become essential tools in navigating the complexity of human health. Loh et al.'s study, with its comprehensive approach and integrative vision, lays the groundwork for future exploration in this exciting and evolving field.

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