

Preview

Answer to the Hamlet-like dilemma of lipid metabolites causing senile macular degeneration

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In this issue of *Cell Reports Medicine*, Han et al.¹ conducted a multi-ancestry genetic and metabolomic analysis to investigate the causal relationships between age-related macular degeneration and plasma and urine metabolites.

As the world's population ages, eye diseases such as age-related macular degeneration (AMD) will continue to be a major cause of vision loss. AMD is caused by the progressive degeneration of photoreceptors due to the accumulation of extracellular deposits, and despite the major advances in understanding its etiology, the underlying pathogenic mechanisms remain incompletely understood.² Thanks to the availability of new resources and technologies, researchers now have the opportunity to access a large amount and a variety of different omics data, which could also be combined together.³ Genomics, the first omics to emerge, focuses on the study of whole genomes, and since 2005, with the advent of genome-wide association studies, more than 30 loci have been associated with AMD.⁴ Another and more recent omics, called metabolomics, quantifies metabolites like carbohydrates, amino acids, and fatty acids. Metabolites are produced by the cumulative effects of the genome and by its interaction with the environment. Therefore, in multifactorial diseases such as AMD, the metabolome may accurately reflect the true functional state of the disease. In support of metabolomics, recent studies have also highlighted its potential for identifying biomarkers in ophthalmic disease.^{5,6} However, no previous study performed a large-scale metabolite-based genome-wide association study across multiple ancestries and biofluids in order to detect AMD-causative metabolites.

In this context, Han et al.¹ conducted an integrative multi-ethnic and multi-fluid

(plasma and urine) metabolomic and genetic study to identify putative causal relationships between metabolites and different AMD subtypes. Using metabolite genome-wide association study, bidirectional two-sample Mendelian randomization and colocalization analyses, Han et al. found 108 putative causal relationships between advanced AMD and plasma metabolites, enriched in the glycerophospholipid metabolism, lysophospholipid, triacylglycerol, and long-chain polyunsaturated fatty acid pathways (Figure 1). The authors also discovered a high concordance of effect sizes between European and Hispanic ancestry populations but a lower concordance between urine and plasma, suggesting limited evidence for urinary metabolites in the context of AMD. Interestingly, in analyses separated by AMD subtype, Han et al. found that most metabolites for advanced AMD were also significantly associated with the choroidal neovascular subtype, which may open new perspectives in understanding potential treatments.

This study represents a comprehensive evaluation of the shared genetic components between metabolites and AMD, also identifying causal factors for AMD. Notably, Han et al. incorporated statistical methods and a wide range of sensitivity analyses to address causality by overcoming the limitations of observational association studies (biased by reverse causation).⁷ Therefore, future studies will need to explore the role of these causal factors in a mechanistic perspective.

Nonetheless, as also highlighted in this study, there are limitations to be consid-

ered, such as the fact that despite the robust identification of biomarkers may indeed provide insight into the pathogenesis of AMD, an individual's biomarker levels are exposed to change over time.⁸ This is a fundamental aspect that needs to be considered. For example, the identification of biomarkers at an early disease stage, when it is often asymptomatic, would also be a valuable contribution to disease management. As little is known about the role that lipid biomarkers may have in predicting AMD risk and how their levels vary during the disease progression, validation of their clinical utility would be essential to translate omics findings into biomarkers. This study also raised the important question about the impact of genetic variation in metabolite measurements on AMD risk in Asian and African populations. Disease risk varies widely between ethnic groups and most of the current studies concern mainly individuals of European descent. It is known that the genomic ancestry can be considered an independent factor, so it is undoubtedly beneficial to investigate whether these differences correspond to an ethnic-specific susceptibility to the disease.⁹ Furthermore, biomarker profiles can vary widely between ethnic groups, and the clinical significance and the implications of these observed differences are still poorly contextualized.

The study by Han et al. demonstrates the advantage of using a genome-wide approach applied to metabolomic data from multi-ethnic and multi-fluid data to reveal putative causal relationships between plasma metabolites and different



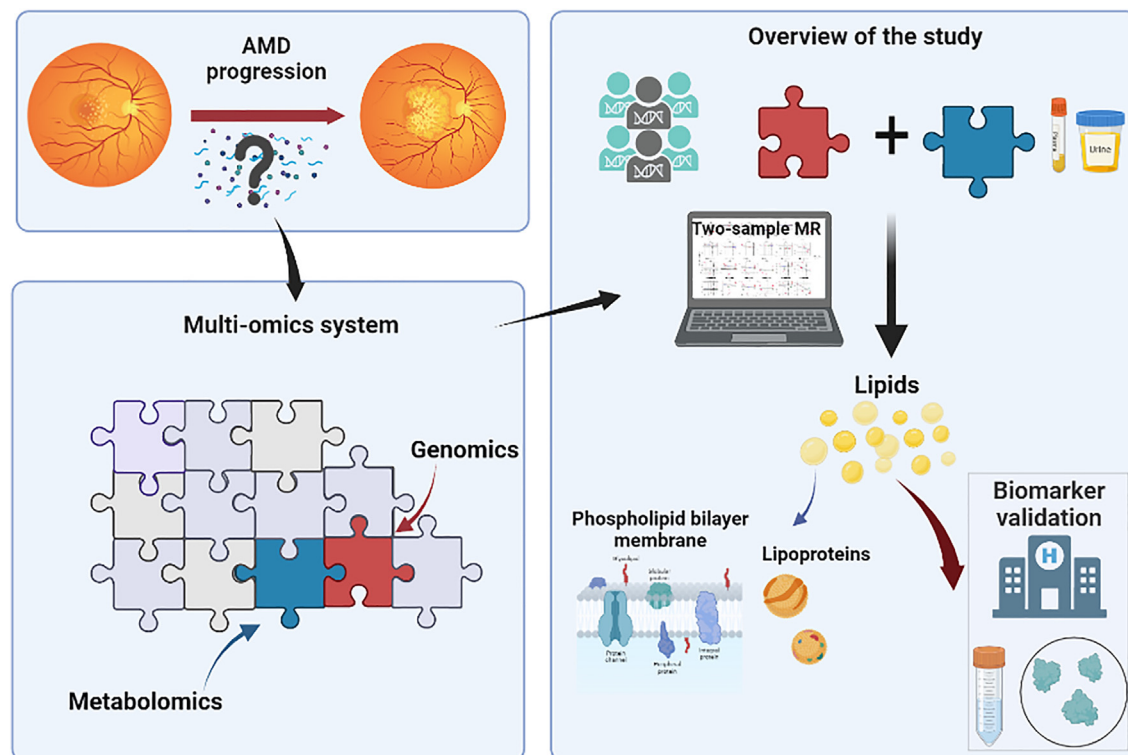


Figure 1. Summary and prospective of the study

Previous studies successfully identified metabolites associated with age-related macular degeneration (AMD), but their causality in a genome-wide approach have not been addressed. Omics technologies, such as genomics and metabolomics, contribute to providing a more holistic view of the pathological processes. The integrative multi-omics approach that combined multi-ancestry metabolomics data (collected from plasma and urine samples) with genomics data, followed by bidirectional Mendelian randomization analyses, provided further biological insights into the causative role of lipid metabolites (i.e., glycerophospholipids, which are also found in biological membranes and lipoproteins). If further validated as AMD biomarkers, lipid metabolites will improve the detection of the disease. Figure created with [BioRender.com](https://www.biorender.com).

AMD subtypes by strengthening the causal role of lipids. Thanks to the efforts of Han et al., the future is open to overcome the current limitations by further evaluating the causal role of lipid metabolites as potential candidate biomarkers for AMD and their eventual implementation in routine clinical care.

DECLARATION OF INTERESTS

The author declares no competing interests.

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