Editorial

Kidney Res Clin Pract 2026;45(1):4-6
pISSN: 2211-9132 • eISSN: 2211-9140
https://doi.org/10.23876/j.krcp.25.150

KIDNEY RESEARCH AND CLINICAL PRACTICE

Toward precision nephrology: identification of cause-specific chronic kidney disease biomarkers through multiomics integration in Korean cohorts

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Chronic kidney disease (CKD) remains a major global health challenge, affecting over 10% of the adult population and contributing significantly to cardiovascular morbidity and all-cause mortality [1,2]. Efforts to improve risk stratification beyond traditional clinical indicators have been limited, primarily because of the heterogeneous etiologies and complex pathophysiological mechanisms underlying CKD. Although numerous efforts, including genome-wide association studies (GWAS) and metabolomic analyses, have been made to identify the risk factors for CKD, these approaches have yet to yield novel or clinically actionable biomarkers for early detection or therapeutic targets [3,4]. Although several multiomics studies on CKD have been performed, research aimed at identifying robust biomarkers specific to disease development and progression remains limited. Notably, few studies have adopted a cause-specific approach that distinguishes between underlying etiologies, such as diabetic kidney disease (DKD), hypertensive nephropathy (HN), and glomerulonephritis. In this context, Kang et al. [5] presented a novel and integrative strategy combining GWAS with targeted plasma metabolomics across two independent Korean cohorts with the goal of identifying etiology-specific biomarkers associated with CKD.

Kang et al.'s two-stage analysis [5] began with a GWAS in the Korean Genome and Epidemiology Study (KoGES) Ansan and Ansung population-based cohorts of >5,000 individuals without baseline CKD. This longitudinal design identified 448 single-nucleotide polymorphisms (SNPs) associated with incident CKD, defined by estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or proteinuria [6]. Findings were validated in a biopsy-proven cohort of 286 individuals from Seoul National University Hospital, grouped by CKD etiology, including DKD, HN, immunoglobulin A nephropathy, and membranous nephropathy (MN). Thirty-six SNP-metabolite pairs were identified, five of which were unique to CKD subtypes. The rs1025170 (near *FOXB1*) and plasma tyrosine pair demonstrated a robust association with DKD progression, highlighting a potential mechanistic link involving sympathetic nervous system dysregulation, as tyrosine is involved in catecholamine synthesis and *FOXB1* in autonomic regulation.

Received: May 26, 2025; **Revised:** June 23, 2025; **Accepted:** June 24, 2025
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Other notable associations include rs1125327 (*ZFP42*) with phosphatidylcholines in DKD, and rs17016322 (*MMRN1*) and rs2295894 (*SYNJ2*) with MN. These findings expand our understanding of the molecular heterogeneity of CKD and support the notion that subtyping CKD based on genetic and metabolic profiles may enhance diagnostic specificity and therapeutic precision [7].

Previous large-scale GWAS efforts, such as the meta-analysis by Stanzick et al. [7] involving over 1.2 million individuals, have significantly expanded the catalog of genetic loci associated with kidney function, fine-mapping hundreds of signals relevant to eGFR and revealing potential mechanistic genes for experimental follow-up. Similarly, a recent GWAS in a Korean population using the KoGES dataset identified over 1,300 loci linked to renal traits and validated numerous variants across multiple biomarkers, emphasizing the value of ancestry-specific analyses [8]. However, while these studies provide essential groundwork, they did not fully explore biomarker specificity across CKD subtypes or integrate metabolomic data to refine causal inference. Methodologically, the use of partial Spearman rank correlation networks in this study allowed the authors to uncover relationships between genomic and metabolomic data layers without relying on preexisting pathway assumptions, a critical advantage in the study of complex, multifactorial diseases such as CKD. Their pathway enrichment analyses further supported the biological plausibility of these findings, revealing dysregulation in arginine-proline metabolism and phospholipid pathways across different CKD subtypes.

Despite the robust integrative approach and novel insights, several limitations remain, as acknowledged by the authors. First, the biopsy cohort was small, particularly disease subgroups such as HN (n = 24), limiting statistical power to detect subtle associations and increasing the risk of type I and II errors. Furthermore, small sample sizes restricted the ability to perform stratified analysis based on comorbidities or treatment status. Second, the study cohort consisted exclusively of Korean participants, limiting its generalizability, as allele frequencies and metabolomic profiles may differ significantly among ethnicities. The use of the KoreanChip and imputation based on the 1000 Genomes and Korean reference panels may have overlooked rare or structural variants important in non-Korean populations. Whole-genome sequencing can complement GWAS data and help address this limitation. Validation in larger multiethnic cohorts is thus critical. Third, metabolomic data were collected at a single time point, precluding assessment of causality. Longitudinal metabolomics can better clarify whether metabolite changes are causative or a consequence of CKD. Fourth, while the correlation-based network analysis identified significant SNP-metabolite associations, no *in vitro* or *in vivo* functional validation was performed. Without mechanistic studies, the biological relevance of these associations remains unclear. Additionally, metabolite selection was partly based on known pathways and curated databases, possibly introducing bias and excluding novel, less-characterized biomarkers. An unbiased, untargeted metabolomic approach may reveal additional or stronger candidate biomarkers.

Nonetheless, several future directions are warranted to advance the translational impact of such integrative analyses in CKD. Validation of the identified biomarkers in independent cohorts with diverse ethnic backgrounds and larger sample sizes is essential for broader clinical applicability. Collecting multiomics data, including metabolomics and transcriptomics, at multiple time points would enable a better understanding of disease progression and causality. Integrative computational models using machine learning could help prioritize biomarker panels, enhancing predictive accuracy beyond individual SNPs or metabolites. Laboratory-based functional studies of the identified variants and metabolites are critical to establish their roles in renal physiology and pathophysiology. Finally, prospective clinical trials are needed to determine whether these biomarkers can improve CKD risk stratification and guide personalized treatment strategies.

In conclusion, this integrative framework provides compelling evidence for the existence of cause-specific biomarkers in CKD. These findings deepen current understanding of CKD pathophysiology and advance the field toward the realization of precision medicine in nephrology. Further studies should validate these biomarkers across diverse populations and examine their utility in clinical settings.

Conflicts of interest

Jong Hyun Jhee is the Associate Editor of *Kidney Research and Clinical Practice* and was not involved in the review

process of this article. The author declares no other conflict of interest.

Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

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