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Review Article

Toward Precision Medicine in Diabetic Kidney Disease: The Call for Integrative Genomic Research in Kazakhstan

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Abstract:

Diabetic kidney disease (DKD) is a major complication of diabetes mellitus and the leading cause of end-stage renal disease (ESRD) worldwide. Despite considerable research efforts, the pathogenesis of DKD remains incompletely understood, largely due to its multifactorial etiology and pronounced phenotypic heterogeneity. Genome-wide association studies (GWAS) have identified over 40 loci associated with DKD; however, these common variants collectively explain only a small fraction of the disease's heritability. Rare and low-frequency variants, often undetected by GWAS, are increasingly recognized as important contributors, and next-generation sequencing (NGS) technologies offer valuable tools for their identification. Kazakhstan, characterized by a unique genetic landscape and substantial ethnic admixture, remains underrepresented in DKD genomics research. Expanding integrative, high-resolution genomic studies in such settings is essential for identifying population-specific risk variants, improving diagnostic accuracy, and advancing precision medicine approaches to DKD prevention and management.

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Diabetic kidney disease (DKD) is a major complication of diabetes mellitus (DM) and the leading cause of end-stage renal disease (ESRD) worldwide (1). DKD develops in approximately 30% of individuals with type 1 diabetes mellitus (T1DM) and in about 40% of those with type 2 diabetes mellitus (T2DM), contributing to a substantial socioeconomic burden on global healthcare systems (2).

The pathogenesis of DKD is highly complex and remains incompletely understood, contributing to ongoing controversies in its clinical management and unsatisfactory patient outcomes. DKD development and progression are driven by a multifactorial interplay of interrelated mechanisms, including hemodynamic and metabolic dysregulation, oxidative stress, activation of the renin–angiotensin–aldosterone system (RAAS), chronic systemic inflammation, and progressive fibrosis (3-5). Notably, the incidence and severity of DKD exhibit considerable ethnic and geographical variation, with markedly higher rates observed in individuals of African descent (three- to six-fold greater), as well as among Mexican Americans and Pima Indians (6). This marked heterogeneity suggests that both modifiable risk factors, such as poor glycemic control, severity of metabolic disturbances, dietary patterns, and socioeconomic conditions, and non-modifiable factors, particularly genetic predisposition and disparities in healthcare access, may collectively influence disease

susceptibility (7). A growing body of clinical evidence supports the role of inherited genetic variants in conferring individual risk for DKD (8).

Several genetic strategies have been used to identify risk loci and genes, including candidate gene analyses, family-based linkage analysis, transmission disequilibrium testing, population-based admixture mapping, and genome-wide association studies (GWAS) (9). The field of human genetics has been revolutionized by the Human Genome Project, which provided a complete map of the human genome and laid the foundation for large-scale genetic association studies (10). GWAS have advanced the identification of common genetic variants contributing to complex diseases, including DKD. GWAS through agnostic scanning of millions of single-nucleotide polymorphisms (SNPs) across the genome have identified 41 loci associated with DKD at genome-wide significance across diverse populations globally (8).

According to a GWAS meta-analysis involving up to 19,406 European individuals with T1DM, 16 loci reached genome-wide significance in association with DKD, with four loci of particular interest located within or adjacent to kidney-function genes, *COL4A3*, *BMP7*, *COLEC11*, and *DDR1* (11). The most prominent association signal was a missense variant in *COL4A3*, rs55703767 (Asp326Tyr), which affects type IV collagen, a key structural component of the glomerular basement membrane. Notably, the minor allele of this variant was associated with a protective effect against DKD, including reduced risk of albuminuria and ESRD, and was further correlated with decreased glomerular basement membrane thickness prior to the onset of clinically detectable kidney damage. A recent GWAS meta-analysis encompassing nearly 27,000 individuals with diabetes, using ten distinct DKD phenotypic definitions, uncovered a novel intronic variant rs72831309 in *TENM2*, which is associated with a reduced risk of both albuminuria and low estimated glomerular filtration rate (eGFR), and exhibits compartment-specific expression effects in kidney tissue (12).

Despite these achievements, current GWAS findings explain only a limited portion of DKD heritability. The limited explanatory power is likely due to the modest effect sizes of common genetic variants and the substantial phenotypic heterogeneity of DKD observed across individuals and populations (8). Increasing evidence indicates that rare and low-frequency variants typically overlooked by conventional GWAS approaches may have a more pronounced impact on disease susceptibility. In this context, next-generation sequencing (NGS) technologies, including whole-exome sequencing (WES) and whole-genome sequencing (WGS), present valuable tools for uncovering such variants, thereby offering deeper insights into the complex genetic architecture of DKD.

NGS has advanced the discovery of novel genetic variants linked to DKD, succeeding through both WGS and WES (13). WES is a genome-wide approach that selectively targets the protein-coding regions of the genome, which are particularly enriched for disease-associated variants (14). Compared to WGS, WES is considered more clinically applicable, as it focuses on nucleotide alterations within exonic regions that encode proteins, areas where the majority of pathogenic variants are typically located (14). A major advantage of WES lies in its ability to generate a more manageable volume of data compared to WGS, which facilitates interpretation while reducing computational demands and cost (14). Despite these benefits, WES can still detect upwards of 100,000 nucleotide variants per individual (15), highlighting the need for robust analytical strategies to distinguish truly pathogenic variants associated with disease phenotypes.

To classify a sequence variant as pathogenic or disease-associated, it should ideally be absent or extremely rare in unaffected control populations and should be predicted to result in a deleterious effect on protein structure or function. Establishing the clinical relevance of such variants is essential to elucidating their role in disease etiology. Both WGS and WES have contributed to the identification of novel biological pathways implicated in DKD pathogenesis, thereby creating a foundation for future therapeutic strategies that may target these pathways or correct underlying genetic defects (16). However, relatively few WES studies have been conducted specifically in DKD (13, 17), and its full po-

tential for diagnosis, risk stratification, and management remains underexplored. Nevertheless, WES holds promise not only for identifying novel etiologic variants related to DKD but also for detecting incidental, clinically actionable mutations that may inform broader aspects of patient care.

There is a growing imperative to undertake comprehensive and context-specific investigations into the pathogenesis of DKD. To date, genetic studies of DKD in Kazakhstan remain limited, despite the country's pronounced ethnic heterogeneity, which may yield distinct genetic profiles compared to populations previously studied. Expanding research efforts in such underrepresented settings is essential for translating genomic discoveries into clinically meaningful interventions and advancing precision medicine in DKD management. Future research should prioritize the inclusion of larger, multi-ethnic cohorts, alongside high-resolution fine-mapping strategies aimed at identifying causal variants. Moreover, the integration of genome-wide data with transcriptomic, proteomic, and metabolomic analyses holds considerable promise for elucidating critical molecular pathways and uncovering novel therapeutic targets.

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