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REVIEW

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Genomic insights into renal diseases: advancements and implications

Nicholas Aderinto[1*], Gbolahan Olatunji[2], Emmanuel Kokori[2], Ikponmwosa Jude Ogieuhi[3], Adetola Emmanuel Babalola[4], Komolafe Babajide Ayodeji[5], Muhammadul-Awwal Irodatullah Bisola[6], Ajekiigbe Victor Oluwatomiwa[1] and Ibukunoluwa V. Ishola[7]

Abstract

Renal diseases pose significant challenges to global health. With conditions like chronic kidney disease (CKD) on the rise, there is an urgent need for deeper insights into their underlying mechanisms and risk factors to improve patient outcomes. Genomic research has emerged as a powerful tool in unraveling the complex genetic architecture of renal diseases, offering opportunities for personalized medicine, early diagnosis, and targeted therapies. This paper provides an overview of recent advancements in genomic research related to renal diseases and their implications for clinical practice. Through genomic analyses such as genomic-wide association studies (GWAS), whole exome sequencing (WES), and functional genomics, researchers have identified numerous genetic variants, metabolic pathways, and molecular mechanisms contributing to different kidney diseases. Furthermore, through functional genomic approaches and polygenic risk scores (PRS), studies have made significant strides in predicting disease risk and stratifying high-risk individuals for early intervention. The integration of genomic insights into clinical practice enables more accurate risk assessment and tailored treatment strategies, although challenges such as genetic heterogeneity and population-specific variations remain. The search for effective biomarkers in nephrology has gained momentum in recent years, driven by the limitations of traditional markers like serum creatinine and the need for more precise diagnostic and prognostic tools. Despite significant progress, challenges remain in translating these findings into clinical practice, including the need for cost-effective validation methods and the integration of genomic data into routine patient care.

Keywords Genomics, Nephrology, Serum biomarkers, Genetic biomarkers, Epigenetic biomarkers

Introduction

Renal diseases include a spectrum of conditions that affect the kidneys, presenting significant challenges to global health [1]. These conditions stem from various complex causes, indirectly impacting global morbidity and mortality by increasing the risks of HIV and malaria infections, hypertension, diabetes, and cardiovascular diseases [1]. In 2015, a study found that reduced glomerular filtration rate (GFR) directly contributed to 1.2 million deaths, 19 million disability-adjusted life years (DALYs), and 18 million years of life lost due to cardiovascular diseases [2, 3]. Specifically, kidney failure claimed the lives of 1.2 million people, marking a 32% increase since 2005 [3]. Renal diseases create a tremendous economic burden

*Correspondence:
Nicholas Aderinto
nicholasoluwaseyi6@gmail.com
[1] Department of Medicine and Surgery, Ladoke Akintola University of Technology, Ogbomoso, Nigeria
[2] Department of Medicine and Surgery, University of Ilorin, Ilorin, Nigeria
[3] Siberian State Medical University, Tomsk, Russia
[4] Faculty of Dentistry, College of Medicine, University of Ibadan, Ibadan, Nigeria
[5] Pearls Specialist Hospital, Lekki, Lagos, Nigeria
[6] Department of Science and Technology, University of Lagos, Lagos, Nigeria
[7] Benjamin S. Carson School of Medicine, Babcock University, Ogun, Nigeria

as high-income countries spend more than 3% of their annual health budget on the management of ESRD [4, 5]. It has also been proposed that by 2030, the need for dialysis use will double from now [4] much of the expenditure, morbidity, and mortality previously linked to diabetes and hypertension are attributable to kidney diseases and their complications [6, 7]. Despite advancements in diagnosis and treatment, many renal diseases remain poorly understood, leading to suboptimal outcomes for patients [8, 9].

Since the inception of genomic integration into nephrology, the understanding of renal diseases as well as their pathogenesis has evolved [10]. Through complex genomic analysis like genomic-wide association (GWAS), whole exome sequencing, and functional approaches to genomics, researchers have been able to identify numerous genetic variants, metabolic pathways, and molecular mechanisms contributing to different kidney diseases [11]. Studies have also been able to elucidate the complexity and heterogeneity of kidney diseases, providing opportunities for personalized medicine, early diagnosis, risk assessment and prediction, and appropriate treatment selection [12, 13]. Moreover, it has been shown the significant potential of genomic testing through nephrology-focused gene panels or exome sequencing to find variants that cause monogenic CKD [14]. These tools are effective in diagnosis and prognosticating renal diseases, allowing disease-specific therapies or clinical trials for monogenic kidney diseases such as Alport syndrome, tuberous sclerosis, Fabry disease, and polycystic kidney disease [15–17]. This paper aims to provide an overview of the recent advancements in genomic research related to renal diseases and their implications for clinical practice.

Methodology

A literature search was conducted using electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar (Table 1). The search strategy utilized a combination of keywords and medical subject headings (MeSH) related to genomic research, renal diseases, and associated terms such as chronic kidney disease (CKD), diabetic nephropathy, glomerulonephritis, genome-wide association studies (GWAS), whole exome sequencing, and functional genomics. The search was restricted to articles published in English language peer-reviewed journals up to March 2024.

Articles were included if they presented original research findings related to genomic insights into renal diseases, advancements in genomic methodologies, or implications of genomic research in clinical practice. Studies focusing on human subjects and involving genetic or genomic analyses of renal diseases were prioritized. Articles were excluded if they were not relevant to the scope of the review, such as those focused solely on animal models, non-genomic aspects of renal diseases, or unrelated topics. Titles and abstracts of identified articles were screened independently by two reviewers to assess eligibility based on the inclusion and exclusion criteria. Full-text articles of potentially relevant studies were retrieved and further evaluated for eligibility. Discrepancies between reviewers were resolved through discussion and consensus.

Table 1 Methodology

Methodology step	Description
Literature search	Conducted using electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Utilized a combination of keywords and medical subject headings (MeSH) related to genomic research, renal diseases, and associated terms. Restricted to articles published in English language peer-reviewed journals up to March 2024
Inclusion and exclusion criteria	Included articles presenting original research findings related to genomic insights into renal diseases, advancements in genomic methodologies, or implications of genomic research in clinical practice. Prioritized studies focusing on human subjects and involving genetic or genomic analyses of renal diseases. Excluded articles not relevant to the scope of the review, such as those focused solely on animal models, non-genomic aspects of renal diseases, or unrelated topics
Screening of titles and abstracts	Independently screened by two reviewers to assess eligibility based on inclusion and exclusion criteria
Full-text evaluation	Potentially relevant studies identified from title and abstract screening were retrieved for further evaluation. Full-text articles were assessed for eligibility
Resolution of discrepancies	Discrepancies between reviewers were resolved through discussion and consensus
Data synthesis	Extracted data were synthesized thematically to provide an overview of recent advancements in genomic research related to renal diseases. Findings were organized according to identified themes, such as genetic variants associated with specific renal diseases, methodologies used in genomic studies, clinical implications of genomic findings, and future directions in the field
Aim of synthesis	Highlighted key insights, trends, and gaps in the existing literature, informing the discussion and interpretation of the findings

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Recent advances in renal genomic research

Traditionally, diagnostic laboratories relied on Sanger sequencing for genetic testing, but the emergence of next-generation sequencing (NGS) has revolutionized the field [18]. Moreover, NGS offers a higher diagnostic yield, particularly beneficial in genetically diverse diseases such as inherited kidney disorders, where multiple genes may be implicated [19]. Besides NGS, other genetic testing modalities such as targeted panels, whole exome sequencing (WES), and whole genome sequencing (WGS) are also playing crucial roles [20]. Meanwhile, emerging research on animal models and novel therapeutic approaches offers hope for future interventions [21]. For example, studies on animal models like the pck rat and the pcy murine model have identified potential therapeutic targets, including vasopressin V2 receptor antagonists and inhibitors of the mTOR pathway, which show promise in reducing renal cyst formation and volumes [22].

Advancements in genomic epidemiology have significantly advanced the comprehension of the genetic underpinnings of renal diseases across diverse populations [23]. Moreover, meticulous examination of DNA sequences among individuals and populations has elucidated specific gene markers contributing to the susceptibility of kidneys to diseases [24]. Additionally, research has pinpointed mutations in the APOL1 gene, particularly prevalent among African Americans, as strongly associated with increased vulnerability to kidney ailments such as focal segmental glomerulosclerosis and chronic kidney disease [25]. Furthermore, studies have uncovered multiple loci contributing to conditions like diabetic nephropathy and IgA nephropathy, underscoring the polygenic nature of these disorders [26, 27]. Similarly, research on the MYH9 gene, prevalent among African American populations, has shed light on its association with non-diabetic end-stage renal disease (ESRD), further highlighting the significant role of genetics in elucidating health disparities [28].

Furthermore, investigations into the interplay between genetic makeup and socioeconomic status have provided crucial insights into health outcomes and disparities. For instance, studies have revealed higher prevalence and mortality rates among African American populations compared to Caucasians, partly attributed to genetic predispositions alongside factors such as limited access to healthcare and diverse lifestyles [29].

Genetic risk factors in renal diseases

Genome-wide studies have been instrumental in identifying genetic risk factors associated with CKD. Moreover, Köttgen and colleagues conducted two large meta-analyses [23]. These comprehensive analyses elucidated 16 loci significantly associated with renal function and CKD. Furthermore, some of these loci were previously linked to renal diseases [23, 24]. Additionally, whole-exome sequencing (WES) enables selective sequencing of protein-coding regions, facilitating the detection of disease-associated variants [25, 27]. Moreover, WES holds promise for uncovering new etiologic genes for nephropathy and detecting incidental mutations unrelated to the primary indications for testing. Similarly, the polygenic nature of renal diseases presents challenges with multiple genetic variants collectively influencing disease susceptibility and progression. Furthermore, functional genomic approaches play a crucial role in unraveling the molecular mechanisms underlying kidney diseases. Moreover, integrating genomic insights into clinical practice enables more accurate stratification and tailored interventions to mitigate disease progression. However, challenges such as genetic heterogeneity and population-specific variations underscore the need for collaborative efforts and data-sharing initiatives to advance our understanding of renal diseases from a genomic perspective.

Biomarker discovery and diagnosis

Serum biomakers

Owing to the limitations of serum creatinine, the most commonly used biomarker of kidney function, different serum and urinary proteins, molecules, and microRNAs have been studied over the past few years as potential biomarkers for renal diseases. Moreover, various biomarkers have been identified for acute kidney injury (AKI), chronic kidney disease (CKD), and diabetic kidney disease (DKD). Additionally, a study by Molinari et al. [30] sheds light on the prognostic value of specific biomarkers in AKI. Furthermore, biomarkers of fibrosis are pivotal for diagnosis and prognosis in CKD. Moreover, specific biomarkers associated with fibrosis include indicators of extracellular matrix remodeling and tissue injury, such as transforming growth factor-β1 (TGF-β1), matrix metalloproteinases (MMPs), collagens (e.g., C1M, C3M, C6M), liver-type fatty acid–binding protein (L-FABP), serum WAP four-disulfide core domain 2 (WFDC2), YKL-40, urinary epidermal growth factor

(uEGF), and transforming growth factor-β1 (TGF-β1) [31–34]. Furthermore, emerging biomarkers like tumor necrosis factor receptor 1 (TNFR1), tumor necrosis factor receptor 2 (TNFR2), fibroblast growth factor 23 (FGF-23), and high-density lipoprotein (HDL) cholesterol offer additional insights into kidney outcomes in patients with type 2 DM [35]. Moreover, several novel biomarkers have emerged as promising indicators of renal diseases, thanks to advancements in genomics and proteomics technologies. Neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule 1 (KIM-1), and interleukin 18 (IL-18) are among the most promising novel AKI/CKD biomarkers under research in humans [36]. NGAL, an early sensitive biomarker for AKI, is an iron-transporting protein that accumulates in kidney tubules and is found in urine after injury [28]. Moreover, higher levels of urinary NGAL have been shown to precede microalbuminuria in patients with type 1 DM [37]. Additionally, KIM-1, a marker of tubular injury, is a type-1 transmembrane protein expressed in the apical membrane of proximal tubular cells in response to renal injury [38]. Furthermore, KIM-1 levels were associated with an increased risk of eGFR decline in persons with early or late DKD [39]. Serum TNFR1 and TNFR2 have also been correlated with renal fibrosis in patients with IgAN, although urinary TNFR1 had a weak correlation [40]. Moreover, patients with moderate to severe TIF had high levels of serum TNFR1 and TNFR2 at the time of renal biopsy, which were associated with disease progression [41]. In addition, TNFR2 levels were the strongest determinants of decline in eGFR in patients with type 1 DM and proteinuria [42]. Similarly, plasma TNFR1 and TNFR2 were the strongest biomarkers in children with glomerulonephritis and congenital defects of the kidney and urinary tract in the CKiD cohort study [43]. The use of cystatin C to estimate eGFR refined risk stratification of CKD patients compared to creatinine-based GFR [44]. Unlike creatinine, cystatin C is less affected by age and muscle mass, making it a more reliable biomarker to assess renal function [45].

Furthermore, a study observed that CKD stage 5 was accompanied by the rising of plasma IL-6. The concentration of IL-18 was also found to negatively correlate with the creatinine clearance, which was concealed by repeated ambulatory peritoneal dialysis [46]. Also, biomarkers of systemic inflammatory response such as IL-8 (CXCL8), IL-34, monocyte chemoattractant protein-1 (MCP-1/CCL2), and macrophage inflammatory protein 1β (MIP-1β/CCL4) [47]. Moreover, high levels of urinary L-FABP predicted the initiation and progression of DKD and all-cause mortality in patients with type 1 DM [48]. Its urinary levels have been linked the extent of tubulointerstitial damage in renal biopsies. It is also helpful in predicting AKI as well as transition from AKI to CKD [49].

WFDC2 has been investigated as a clinical prognostic biomarker for kidney disease and fibrosis. Moreover, the fibrosis index, which combines WFDC2 and Serum matrix metalloproteinase 7 (MMP-7) levels, is strongly linked to renal decline regardless of albuminuria status [50]. Additionally, urinary YKL-40 has been associated with eGFR decline and incident composite renal outcomes over time in hospitalized patients [51]. EGF plays roles in renal tubulogenesis and tubular regeneration after injury, and decreased uEGF levels have been correlated with TIF [52]. Furthermore, collagens II and III accumulate in the early phases of kidney fibrosis development, while type IV, a component of the basement membrane, serves as a marker of glomerulosclerosis and interstitial fibrosis. Other ECM proteins, such as fibronectin, nestin, TSP-1, and vimentin, may also serve as kidney fibrosis markers [51]. Moreover, MMP-2, MMP-8, and MMP-9 have been found elevated in CKD and diabetic patients, correlating with serum phosphate, FGF-23, and proteinuria levels [48]. Additionally, proteins like fetuin-A, plasma copeptin, secreted frizzled-related protein 4, IGFBP7 x TIMP-2, calprotectin, urinary angiotensinogen, and urinary microRNA are under investigation as potential biomarkers for renal diseases [47] (Table 2).

Genetic biomarkers

Genetic biomarkers have been identified by several studies that revealed significantly differentially expressed genes (DEGs) or differentially expressed micro RNAs (DEmiRNAs) between patients and controls [60]. Polymorphisms in the gene region rs4293393, which codes for uromodulin (Tamm-Horsfall protein), have been linked with an increased risk of CKD [61]. Other SNPs that exerted similar prediction of CKD onset include protein kinase AMP-activated non-catalytic subunit gamma 2 (PRKAG2), longevity assurance gene homologs (LASS2), disabled homolog 2, dachshund family transcription factor 1 (DACH1), and stanniocalcin 1 (STC1) [62].

Serum creatinine (SCr), eGFR, and urinary albumin-to-creatinine ratio have been researched into using GWAS in different etiologies of CKD and ESRD [63]. Several genetic variants have been linked with CKD, some of which are implicated in the pathogenesis of CKD. Even though various genetic loci have been associated with CKD, the most widely reported and replicated variants lie within the *UMOD* gene. Mutations in *UMOD* have been associated with autosomal dominant tubulointerstitial kidney disease that can progress to CKD [61]. Additionally, contiguous *COL4A5-COL4A6* gene deletions have been shown to be responsible for the very rare

Table 2 Overview of biomarkers in renal diseases

Biomarker type	Biomarkers	Description
Serum biomarkers	- *TIMP-2*×*IGFBP7* [53]	Urinary biomarker combination associated with increased mortality risk in acute kidney injury (AKI) patients
	- *TGF-β1*, *MMPs*, *Collagens*, *L-FABP*, *WFDC2*, *YKL-40*, *uEGF* [54]	Biomarkers of fibrosis in chronic kidney disease (CKD), providing insights into fibrosis extent and progression
	- *TNFR1*, *TNFR2*, *FGF-23*, HDL cholesterol [55]	Novel biomarkers in diabetic kidney disease (DKD), offering additional insights into kidney outcomes in patients with type 2 diabetes mellitus
	- *NGAL*, *KIM-1*, *IL-18* [56], *IL-6* [40], *IL-8*, *IL-34*, *MCP-1*, *MIP-1β* [51], *L-FABP* [57], *WFDC2* [58]	Emerging biomarkers for AKI/CKD, showing associations with disease progression, renal replacement, and severity of pathology
Genetic biomarkers	- SNPs associated with CKD and ESRD [24], *UMOD* [29], *PRKAG2*, *LASS2*, *DACH1*, *STC1* [15]	Genetic variants linked with high CKD risk or worse prognosis, offering insights into disease onset and progression
	- *WT1*, *NPHS1*, *NPHS2*, *ADCK4*, *IFT144* [29], *SMOC2*, *APOL1* [36], *KCNJ1* [37], *COL4A5-COL4A6* [40]	Genetic associations with specific renal diseases such as congenital nephrotic syndrome, IgA nephropathy, and Alport syndrome, providing insights into disease mechanisms
Epigenetic biomarkers	- miRNAs, DNA methylation [42], histone modifications [19]	Epigenetic markers useful in predicting CKD severity, differentiating between CKD stages, and evaluating ESRD risk, offering insights into renal disease progression and severity
Challenges and potential applications	- Costs of validation, lack of prioritization criteria [11], sample preparation challenges [12], analytical and biological variation [59]	Challenges in biomarker validation and clinical implementation, including high costs, lack of prioritization criteria, difficulties in sample preparation, and issues with analytical and biological variation, along with the potential applications of novel approaches, international collaborations, and functional studies in overcoming these challenges

occurrence of Alport syndrome with leiomyomatosis which affected male severely as compared to female individuals [62]. Chaudhary et al. identified the interaction between *SMOC2* and *APOL1* in the development of progressive CKD through a genome-wide association study. *WT1* variant was associated with IgA nephropathy, and *KCNJ1* was reported by Tian et al. to be associated with Barter syndrome type II. It was demonstrated that all attributable risk for CKD of the *APOL1* locus was associated with SNPs in the last exon of the adjacent *APOL1* gene, and this showed a strong association with non-diabetic CKD and FSGS. *MYH9* gene has also been studied to be closely linked to monogenetic FSGS [60].

Epigenetic biomarkers

Epigenetic biomarkers, specifically microRNAs (miRNAs), play a crucial role in kidney fibrosis and renal disease progression. These are short (21–23 nucleotides long) endogenous antisense non-coding RNAs that function as post-translational repressors of gene expression. miRNAs regulate kidney fibrosis by hampering or stimulating matrix gene expression and modulate systemic and intra-renal inflammatory response through TGF-β signaling [63]. High levels of *miR-21* target PTEN, PDCD4, and RECK, which are involved in cell proliferation and apoptosis regulation, indicating its role as a marker for ESRD development. *miR-92* acts similarly to *miR-21*, indicating fibrosis and ESRD progression by targeting integrin α5 and MMP2. Elevated levels of *miR-192* have been observed in cultured mesangial cells and glomeruli of diabetic mice, suggesting a role in diabetic nephropathy. *miR-192* targets ZEB1 and ZEB2, which are involved in epithelial-to-mesenchymal transition. Lowering renal *miR-192* levels led to decreased renal fibrosis and improved proteinuria [57]. *miR-181a* targets BCL-2 and Notch signaling pathways, indicating its potential as a biomarker for CKD progression [64]. Additionally, *miR-122* and *miR-95* have been studied as biomarkers, with *miR-122* targeting cyclin G1 and *miR-95* involved in cellular stress responses. These miRNAs collectively offer a broad spectrum of targets and mechanisms that underscore their utility in renal disease diagnostics and prognostics [58].

Since DNA methylation correlates with kidney pathologies, it can be useful as a biomarker to predict the risk of development of CKD/ESRD as well as the degree of their severity. 5-Methyl-2′-deoxycytidine (5-Me-dC), combined with macroalbuminuria or α1-microglobulin (α1m) in urine, predicts end-stage CKD. Decreased methylation of the P66shc promoter in peripheral blood mononuclear cells is associated with an increased risk of cardiovascular death in ESRD patients [55]. The appearance of the combination of 5-methyl-2′-deoxycytidine (5-Me-dC) and macroalbuminuria or α1-microglobulin (α1m) in urine predicts end-stage CKD. Higher DNA methylation levels in the calcitonin (CALCA) promoter

have been observed in the urine of kidney transplant patients compared to controls. Abnormalities of methylation in the tissue of patients with ADPKD were shown by Xu et al. in a study [62]. Increased methylation in the promoter of the renal kallikrein (KLK1) gene has been found in blood and urinary DNA from acute kidney injury (AKI) patients compared to healthy controls [56]. Furthermore, DNA methylation patterns in genes such as RASAL1 and KLOTHO have been linked to renal fibrosis and aging-related kidney diseases, respectively, highlighting the extensive role of methylation in various renal pathologies [65].

These histone modifications can indicate disease progression and severity, providing insights into the molecular mechanisms of renal pathologies [65]. For example, acetylation of histone H3 at lysine 9 (H3K9ac) and methylation of histone H3 at lysine 4 (H3K4me3) have been associated with active transcription in kidney cells, while methylation of histone H3 at lysine 27 (H3K27me3) is linked to gene repression in renal fibrosis [66]. Understanding these modifications helps in deciphering the complex regulatory networks involved in CKD and ESRD, paving the way for potential therapeutic interventions targeting epigenetic modifications [67].

Challenges and potential applications of biomarker discovery in nephrology

Obtaining human renal tissue for gene expression analysis remains a daunting task. Biopsies taken for routine diagnostic and staging purposes exist as majorly as formalin-fixed, paraffin-embedded (FFPE) specimens even though many researchers today use either frozen biopsy sections or RNA later preserved biopsies at low temperatures for sample preparation so as to curtail loss and degradation of RNA. Moreso, the chemical crosslinking of RNA and subsequent fragmentation of RNA during isolation have made the extraction of RNA from FFPE tissue a difficult process [60].

The current bottlenecks that surround the application of genetic biomarkers in routine clinical practice will be overcome by emerging novel approaches, increasing interest in genomics, growing international collaborations, extensive functional studies, and integration of multi-level information [60].

Genomic editing and gene therapy

Genomic editing involves targeted alterations of specific sections of the human genome to manage diseases, while gene therapy aims to treat or prevent diseases by correcting underlying genetic issues, often involving the incorporation of engineered genetic materials into the host genome at the cellular level [68]. Renal replacement therapies like dialysis and renal transplantation are currently the mainstay treatments for renal diseases. However, advancements in scientific research and technology drive the demand for more effective treatments with fewer limitations [69]. Approximately 30% of chronic kidney diseases have a hereditary basis, making them suitable targets for cell or gene therapy before the development of irreparable renal failure [69]. While acquired causes like hypertension and diabetes contribute to chronic kidney disease, inherited conditions such as Alport syndrome, gene therapies have shown promise in preventing the manifestation of these conditions by identifying genetic carriers and asymptomatic patients [70].

Gene editing, a complex yet effective component of gene therapy, encompasses various tools like CRISPR-Cas9, TALENs, and ZFNs [71]. CRISPR, discovered in 2012, offers a novel approach to gene editing and therapy, with the Cas9 nuclease anchored to an RNA fragment that base pairs with the target DNA sequence [72]. One example of potential application is in transthyretin amyloidosis (ATTR), implicated as an acquired systemic cause of chronic kidney disease due to abnormal deposition of Transthyretin fibrils in the kidney [73]. CRISPR-Cas9 therapy for ATTR amyloidosis could intercept the disease at its early stages, preventing renal manifestations. NTLA-2001, a novel intravenous CRISPR-Cas9 treatment, targets and edits the TTR gene in hepatocytes, thereby reducing both wild-type and mutant TTR levels with a single dosage [73]. However, ethical concerns raised by institutions like the National Institute of Health (NIH) highlight risks such as off-target effects and mosaicism, necessitating cautious consideration of the technology's uncertainties and implications [74].

Targeting renal gene therapy poses unique challenges due to the kidney's complex structure, comprising numerous specialized cell types and intricate filtration systems [69]. Somatic cell therapy, targeting non-reproductive cells, offers a conservative approach with limited impact beyond the treated individual, but its effects may be temporary, requiring repeated treatments [75]. While gene therapy holds promise for managing renal diseases, accessibility remains a concern due to high costs, limiting its widespread adoption. Safety considerations, including the risk of off-target effects, underscore the need for informed consent and vigilant monitoring [75].

Looking ahead, genomic editing and gene therapy offer significant potential for addressing both inherited and acquired renal conditions, with advancements in

technology driving personalized treatments tailored to individual genetic profiles [76, 77].

Mechanistic aspect of genomics related to CKD and renal diseases

The development of chronic kidney disease and renal disease has been linked to an interplay between genetic and environmental factors. Genomic sequencing provides an insight into the mechanism underlying these renal conditions [78]. Genomics aids in understanding the molecular processes involved in the etiology of renal disorders. The RAAS pathway is crucial in the development of renal diseases, In a case–control investigation involving individuals from the South Indian population, a correlation was established between diabetic nephropathy (DN) patients and individuals without the condition, focusing on the ACE insertion/deletion (ID) and NOS3 variable number tandem repeat (VNTR) polymorphisms [79].

The study revealed a noteworthy link between the DD genotype of the ACE gene and the progression of chronic kidney disease (CKD) in diabetic nephropathy patients [79].

Transporter proteins are essential for drug absorption and excretion in the kidney. Genetic differences in the genes that encode these transporters, such as organic anion transporters (OATs) and organic cation transporters (OCTs), can have an influence on drug clearance in the kidney [80]. Polymorphisms in transporter genes can have an impact on pharmacological effectiveness and toxicity, especially for medicines that are largely excreted through the kidney [81].

Clinical Implementation, challenges, and future directions

Translating genomic research findings into clinical practice in nephrology presents significant challenges. According to Chalmers and Glasziou's analysis, a staggering 85% of health-related research fails to create a relevant impact, underscoring the crucial need for translational health experts to bridge the gap between research discoveries and practical applications [82]. Many institutions, including hospitals, universities, and colleges, are recognizing the importance of translational health sciences in incorporating research findings into achievable clinical steps [83].

Additionally, accuracy issues in adult populations, compared to younger cohorts, complicate the application of genomics [84]. Despite the reduction in DNA sequencing costs since the Human Genome Project, the expense of genomic technology remains substantial, requiring considerable financial and human capital [84]. However, studies suggest that the long-term benefits of genomic interventions may outweigh the costs of managing chronic renal diseases [71].

The "One Health" concept, which emphasizes the interconnectedness of human, animal, and environmental health, could play a significant role in nephrology. A pilot study in Sri Lanka identified a multifactorial association between pet ownership, household pests, and CKD, highlighting the importance of considering environmental factors in disease management [54].

Conclusion

Renal diseases represent a pressing global health challenge, with conditions such as chronic kidney disease (CKD) increasingly affecting populations worldwide. The imperative for a deeper understanding of their underlying mechanisms and risk factors is paramount to enhancing patient outcomes. Genomic research has emerged as a crucial avenue in unraveling the intricate genetic landscape of renal diseases, offering promising prospects for personalized medicine, early detection, and targeted therapies. This paper has provided an insightful overview of recent strides in genomic research pertaining to renal diseases and their direct implications for clinical practice. Through methodologies like GWAS, WES, and functional genomics, researchers have identified a plethora of genetic variants, metabolic pathways, and molecular mechanisms contributing to various kidney diseases. Moreover, the application of functional genomic approaches and PRS has notably advanced in predicting disease susceptibility and stratifying individuals at heightened risk for early intervention. The integration of genomic insights into clinical settings holds the potential to revolutionize risk assessment and treatment strategies, offering tailored approaches to patient care. However, challenges such as genetic heterogeneity and population-specific variations underscore the complexity of translating genomic findings into actionable clinical protocols. Furthermore, the quest for effective biomarkers in nephrology has gained momentum, driven by the inadequacies of traditional markers like serum creatinine and the pressing need for more precise diagnostic and prognostic tools. Despite remarkable progress, hurdles persist in the seamless integration of genomic data into routine patient care, necessitating the development of cost-effective validation methods and streamlined protocols for clinical implementation.

Abbreviations

AKI	Acute kidney injury
CKD	Chronic kidney disease
ESRD	End-stage renal disease
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
TIMP-2	Tissue inhibitor of metalloproteinases 2
IGFBP7	Insulin-like growth factor binding protein 7
TNFR1	Tumor necrosis factor receptor 1
TNFR2	Tumor necrosis factor receptor 2
FGF-23	Fibroblast growth factor 23

HDL	High-density lipoprotein
NGAL	Neutrophil gelatinase-associated lipocalin
KIM-1	Kidney injury molecule 1
IL-18	Interleukin 18
WFDC2	Serum WAP four-disulfide core domain 2
uEGF	Urinary epidermal growth factor
TGF-β1	Transforming growth factor-β1
MMPs	Matrix metalloproteinases
L-FABP	Liver-type fatty acid-binding protein
SNPs	Single-nucleotide polymorphisms
GWAS	Genome-wide association studies
5-Me-dC	5-Methyl-2′-deoxycytidine
ADMA	Asymmetric dimethylarginine
SDMA	Symmetric dimethylarginine
miRNAs	MicroRNAs
DNMTs	DNA methyltransferases
ATTR	Transthyretin amyloidosis
CRISPR	Clustered regularly interspaced short palindromic repeats
TALENs	Transcription activator-like effector nucleases
ZFNs	Zinc finger nucleases
ADPKD	Autosomal dominant polycystic kidney disease
AI	Artificial intelligence

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Authors' contributions
NA conceptualized the study; all authors were involved in the literature review; GO and NA extracted the data from the reviewed studies; all authors wrote the final and first drafts. All authors read and approved the final manuscript.

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Declarations

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