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Review

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Genomic biomarkers for chronic kidney disease: the first step towards personalized medicine?

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Abstract

With the prevalence of end stage renal disease steadily increasing, chronic kidney disease (CKD) represents an impending public healthcare challenge. Classical diagnostic biomarkers of CKD, including creatinine, have low sensitivity and specificity. Thus, novel diagnostic and prognostic biomarkers for patients at high risk of early-stage progression are urgently needed. Personalized medicine approaches generally stratify patients according to their biological or genomic make-up. Targeted clinical trials require more precise identification of these subgroups. The use of new biomarkers obtained via high-throughput technologies is expected in future, accompanied by vast improvements in computational power applied in genomics, proteomics, and metabolomics studies using biological fluids and renal biopsy tissue. Genomic biomarkers may not only provide additional information regarding the etiology and mechanisms underlying CKD progression, but may also enable early diagnosis and the selection of appropriate drugs, thereby personalizing therapy. This review discusses commonly used research methods in genomic medicine and summarizes currently available genomic biomarkers in inherited and acquired CKD.

Keywords: Genomics, biomarkers, chronic kidney disease, personalized medicine, end-stage renal disease, high-throughput technology

INTRODUCTION

Chronic kidney disease (CKD), characterized by kidney damage and/or a decreased estimated glomerular filtration rate (eGFR) over a period of at least 3 months, imposes a drastic public health burden worldwide[1]. CKD of various origins commonly proceeds through the renal fibrosis pathway, resulting in end-stage renal

disease (ESRD)[1]. In 2015, 124,411 new patients were diagnosed with ESRD according to the United States Renal Data System, reflecting the increasing burden of kidney failure[2]. A possible explanation for increased renal failure is that the symptoms of most patients are non-specific or even missing in early-stage CKDs (stages 1 to 3). Therefore, timely diagnosis and treatment of patients at a high risk of progression in the early stage is a major clinical concern.

A biomarker is a quantifiable and analyzable characteristic that serves as an indicator of disease status, prognosis or response to therapeutic interventions[3]. Proteinuria and kidney function parameters are reliable and relatively non-invasive classical biomarkers; however, their sensitivity and specificity in detecting early renal injury is not optimal[4]. Moreover, they cannot provide pathological information at the molecular level. Therefore, there is an urgent need to uncover novel biomarkers with high sensitivity and specificity.

Personalized medical approaches generally stratify patients based on their biological or genomic make-up and thus optimize personalize management regimes. The genetic background has a strong influence on a wide spectrum of CKDs. Therefore, genomic biomarkers are expected to provide additional information regarding the etiology and mechanisms underlying CKD progression, as well as help identify more homogeneous patient subgroups and increasingly targeted therapies[5]. The use of new biomarkers obtained via high-throughput technologies is expected in the future, together with vast improvements in computational power applied to genomics, proteomics, and metabolomics studies using biological fluids and renal biopsy tissue[6]. So far, such studies have focused on optimzing development of new therapies, drug selection and drug dosage[7].

The aim of personalized medicine is to enable clinicians to rapidly, efficiently and accurately determine the most appropriate diagnosis and therapy for a patient[8]. Genomic biomarkers may not only provide information regarding the etiology and mechanisms underlying CKD progression but may also be used for early diagnosis and for the selection of appropriate drugs, thereby personalizing therapy.

In this review, we first introduce commonly used genomic medicine methods. Then, we summarize the potential genomic biomarker candidates of inherited and acquired CKD. Finally, we discuss the opportunities and challenges offered by personalized genomic medicine.

OVERVIEW OF GENE VARIATIONS AND GENETIC TESTING

According to databases including Gencode, Ensembl and RefSeq, there are approximately 19,000 to 21,000 protein-coding genes in the human genome[9]. Moreover, all humans share approximately 99.9% similarity in their DNA[10].

Nucleotide-level variations occur frequently in the human genome, the most common being a single-nucleotide polymorphism (SNP), which is a variation in a single nucleotide between genome sequences. Laboratories use high-throughput whole genome sequencing for genotyping of all SNPs in an individual. SNPs are present at > 1% within a given population and account for a majority of normal human genetic variations[11]. Most SNPs have no obvious phenotypic effects, although some can affect gene expression and susceptibility to certain diseases[12]. Earlier methods for genome screening for genetic etiologies of disease employed candidate gene studies and linkage analysis. In 2005, the first genome-wide association study (GWAS) was performed[13]. Since then, GWASs have emerged as the most widely used tools to map risk-associated loci for complex pathologies via analysis of the association between genome-wide markers and the disease.

Even though genetic predisposition of an individual is a critical factor in determining renal disease manifestation, robust interactions between genetic predisposition and environmental factors strongly influence the course of CKD. Only a few renal disorders, such as Alport syndrome (AS) and autosomal dominant polycystic kidney disease (ADPKD), are caused by single-gene variations. Such disorders can

be diagnosed via mutation analysis, and their clinical manifestations are similar among patients, although variants in other genes may influence or modify disease course and severity[14].

For multifactorial kidney diseases with complex causal relationships and poorly understood mechanisms of action, such as diabetic nephropathy (DN) and hypertensive nephrosclerosis, disease course and the rate of progression to ESRD vary substantially among patients. Over the past decade, rapid advances in genetics have raised expectations for a switch from traditional medical diagnosis and treatment towards personalized medicine. Numerous genetic variants have been implicated in studies of CKD. Herein, we review the current genomic biomarkers in inherited and acquired CKD.

EMERGING GENOMIC BIOMARKERS FOR INHERITED CKD

AS

AS is an inherited disease caused by mutations affecting collagen type IV (specifically, *COL4A3* and *COL4A4* on chromosome 2 and *COL4A5* on chromosome X) in the glomerular basement membrane (GBM). It is characterized by kidney damage, hearing loss, and eye abnormalities[15,16]. Almost all patients experience hematuria and proteinuria at symptom onset. AS occurs in approximately 1 in 50,000 neonates and men are more likely to be symptomatic than women[17]. Moreover, it accounts for > 1% of patients receiving renal replacement therapy[15]. Genetic testing has generally replaced rather invasive procedures such as kidney or skin biopsy, and can yield an accurate diagnosis in approximately 95% of AS patients[18].

In 80%-85% of cases, AS is inherited in an X-linked manner (XLAS) and is caused by mutations in *COL4A5*. Additional, inheritance patterns include autosomal recessive AS (ARAS) manner, or, less commonly, autosomal dominant AS (ADAS) owing to mutations in *COL4A3* or *COL4A4*[19].

Cervera-Acedo *et al.*[19] assessed a Spanish family with variable phenotypes of ADAS via clinical, histological, and genetic analyses. They reported that carriers of p.G333E and p.P1461L or p.S1492C mutations in *COL4A3* presented an earlier onset of disease than individuals, who carried only the p.G333E mutation. Fu *et al.*[20] reported that a synonymous p.Gly292Gly mutation in XLAS could alter the splicing donor site of *COL4A5*.

Targeted capture and next-generation sequencing allowed Liu *et al.*[21] to detect 15 novel mutations, 6 known mutations, as well as 2 novel fragment deletions in the genomes of 20 patients with AS from unrelated Chinese families. Weber *et al.*[22] identified 47 novel mutations in AS and thin basement membrane nephropathy (TBMN) patients through an assessment of 216 individuals. Guo *et al.*[23] reported that the intron mutation c.4127+11C>T and missense mutation c.4195A>T in *COL4A4* were possible causes of ADAS [Table 1].

These results broadened our understanding of mutations in 3 different collagen type IV genes, which have important implications as genomic biomarkers in diagnosis, prognosis, and genetic counseling. Further studies are expected to elucidate the correlations between these novel identified genetic mutations and the resulting phenotypes.

TBMN

Collagen type IV-related nephropathies include another disorder closely resembling AS, referred to as TBMN. Also called benign familial hematuria, TBMN is characterized by persistent hematuria, minimal proteinuria, normal renal function, and a uniformly thinner GBM[24,25]. Despite the fact that TBMN does not require treatment, its exact diagnosis is still important because its clinical findings overlap with those of early AS.

In contrast to AS, TBMN is usually caused by heterozygous mutations of *COL4A3* or *COL4A4* with the carrier having ARAS. Several novel mutations of these two genes have been reported as pathogenic in recent years. Hou *et al.*[26] reported that a novel mutation (3725G>A, G1242D) in *COL4A3* resulted in TBMN

Table 1. Genome-wide association studies of inherited chronic kidney disease

Diseases	Sample size	Study population	Main findings	References
AS	A family	Spanish	In ADAS, carriers of p.G333E and p.P1461L or p.S1492C mutations in *COL4A3* have an earlier onset of disease than those of only p.G333E mutation	[19]
AS	A family	Japanese	A synonymous p.Gly292Gly mutation in XLAS can alter the splicing donor site of the *COL4A5* gene	[20]
AS	20 patients	Chinese	Detected 15 novel mutations and 6 known mutations	[21]
AS	216 patients	European	Identified 47 novel mutations in AS and TBMN	[22]
AS	A family	Chinese	The intron mutation c.4127+11C>T and missense mutation c.4195A>T in *COL4A4* were possible causes of ADAS	[23]
TBMN	A family	Chinese	A novel mutation (3725G>A, G1242D) in COL4A3 resulted in TBMN pathogenesis	[26]
TBMN	A family	Chinese	Identified a novel heterozygous splicing mutation in *COL4A4* (c.1459+ 1G>A)	[27]
TBMN	45 patients	Korean	Identified 2 potential pathogenic variants, G199R and G1606E, along with another 6 novel variants	[28]
TBMN	A family	Cypriot	Mutations in *COL4A1* collagen type IV α1 chains could also cause TBMN	[29]
ADPKD	A family	Chinese	Identify a novel heterozygous frameshift mutation c.3976_3977insCT (p.F1326Sfs*21) in *PKD1*	[30]
ADPKD	A family	Chinese	Reported a novel frameshift mutation, c. 12605_12632del28, in *PKD1*	[35]

AS:Alport syndrome; ADAS: autosomal dominant AS; XLAS: X-linked AS; TBMN: thin basement membrane nephropathy; ADPKD: autosomal dominant polycystic kidney disease

pathogenesis within an identical family. Xu *et al.*[27] identified a novel heterozygous splicing mutation in *COL4A4* (c.1459+1G>A), which might be responsible for TBMN. Baek *et al.*[28] investigated the sequence of full-length *COL4A4* in 45 Korean TBMN patients and identified 2 potential pathogenic variants, G199R and G1606E, along with another 6 novel variants. Interestingly, mutations in other genes may still contribute to TBMN. Gale *et al.*[29] performed genome-wide linkage analysis, whole-exome sequencing, and co-segregation analyses on 20 family members and reported that mutations in *COL4A1* collagen type IV α1 chains could also cause TBMN [Table 1]. Given these findings, a combination of genetic testing and immunofluorescence analysis appears most suitable to guarantee an exact diagnosis.

ADPKD

ADPKD is the most prevalent monogenic renal disease. It is characterized by the development of renal cysts, which chronically impair kidney structure and function. It is estimated that approximately 50% of patients with ADPKD eventually develop ESRD[30]. ADPKD is reportedly associated with mutations in polycystin-encoding genes *PKD1* and *PKD2*, with *PKD1* mutations having been reported in up to 85% of patients[31]. In 2016, the rare third gene encoding glucosidase II alpha subunit (*GANAB*) at position 11q12.3, was reported and estimated to account for 0.3% of cases[32,33].

To date, more than 1,200 and 200 pathogenic germline mutations in *PKD1* and *PKD2*, have been archived in the Mayo PKD database[34], and the numbers are still increasing. For instance, targeted exome sequencing of *PKD1* and *PKD2*, allowed Sha *et al.*[30] to identify a novel heterozygous frameshift mutation c.3976_3977insCT (p.F1326Sfs*21) in *PKD1*. Wang *et al.*[35] reported a novel frameshift mutation, c.12605_12632del28, in *PKD1* in a Chinese family with ADPKD [Table 1].

Genetic testing is currently applied to assess patients with atypical radiologic presentations or a negative family history. With decreasing costs and faster sequencing speed, its clinical use may be expanded to indicate prognosis and guide patient management in the near future.

EMERGING GENOMIC BIOMARKERS FOR ACQUIRED CKD

Idiopathic membranous nephropathy

Idiopathic membranous nephropathy (IMN) is an immune complex-mediated disease and represents a common cause of glomerulonephritis. Gene sequencing and GWASs have yielded major breakthroughs regarding IMN biomarkers in recent years.

Stanescu *et al.*[36] reported two loci, phospholipase A2 receptor 1 (*PLA2R1*) and human leukocyte antigen (*HLA*)-*DQA1*, strongly associated with IMN risk among 556 European patients. The associations were further strengthened when the two loci were evaluated simultaneously. These findings are consistent with the fact that the *PLA2R1*-encoded protein, M-type PLA2R1, is the major autoantigen in humans with IMN. Moreover, a large cross-sectional study involving over 2000 Chinese individuals detected anti-PLA2R antibodies in 73% of subjects, who carried both risk alleles but none in those with no mutation in these two genes, suggesting that the interaction between *PLA2R1* and *HLA-DQA1* variants contributes to the presence of anti-PLA2R antibodies[37]. Interestingly, Sekula *et al.*[38] reported that mutations in *PLA2R1* were specific to IMN, whereas *HLA-DQA1* variants (encoding major histocompatibility complex, class II, DQ alpha 1) were also associated with other kidney diseases including type 1 DN, lupus nephritis and focal segmental glomerular sclerosis (FSGS) in adults. By sequencing the entire major histocompatibility complex region in over 200 DNA samples, Le *et al.*[39] reported a strong association between PLA2R-related IMN and HLA-DRB1*15:01 and HLA-DRB3*02:02 alleles in the Chinese population. How exactly mutations in *PLA2R* finally result in the generation of anti-PLA2R antibodies remains to be elucidated [Table 2].

Anti-PLA2R1 antibodies are detected in nearly 70% of patients with IMN. Measurement of anti-PLA2R antibodies has been translated into clinical practice for diagnosing IMN, and emerging studies indicate it can also be used to predict the response to immunosuppressive therapy and long-term outcomes[40]. Considering that genetic mutation is an upstream event, detection of risk variants might provide early diagnostic and prognostic information on IMN[41,42]. However, long-term prospective studies are still required to establish the statistical likelihood of individuals with high-risk genotypes developing IMN over their lifetime.

IgA nephropathy

IgA nephropathy (IgAN) is a major cause of renal failure worldwide. IgAN perfectly exemplifies how multiple gene interactions can affect kidney injury because the combined distribution of risk-associated alleles strongly correlates with its geographic prevalence gradient; it is highest in Asian, intermediate in European, and lowest in African countries[43]. In the past 5 years, several reviews and meta-analyses have discussed GWAS findings for IgAN[44-48].

The increasing number of larger GWASs in different populations has unveiled numerous IgAN-associated loci, including complement factor H-related (*CFHR*) genes[49-51], or those encoding defensing (*DEFA*)[47,52], *HLA*[53], sprouty RTK signaling antagonist 2 (*SPRY2*)[54], vav guanine nucleotide exchange factor 3 (*VAV3*)[46], core 1 synthase, glycoprotein-*N*-acetylgalactosamine 3-beta-galactosyltransferase 1 (*C1GALT1*)[55], and tumor necrosis factor superfamily member 13 (*TNFSF13*)[56].

In 2010, Feehally *et al.*[53] reported a genome-wide analysis in an IgAN cohort selected from the UK Glomerulonephritis DNA Bank. Their results suggested that the *HLA* locus contained the strongest common susceptibility alleles responsible for genetic predisposition to IgAN in the European population. Factor H, a component of the alternative pathway, is present in the mesangial immune deposits, which can be activated by IgA1, and contributes to IgAN progression[57]. Gharavi *et al.*[49] performed targeted follow-up evaluations in Chinese and European cohorts including 1,950 patients and 1,920 controls, and detected a common deletion in *CFHR1* and *CFHR3* at position 1q32 and a locus at position 22q12 in IgAN individuals. Deletions in *CFHR1* and *CFHR3* were related to a reduced risk of IgAN. In contrast, Jullien *et al.*[50] reported deletion variants of *CFHR1* and *CFHR3*, which were associated with mesangial immune deposits but not with IgAN progression. Zhai *et al.*[51] recruited 500 IgAN patients and 576 healthy controls and sequenced all exons, intronic flanking regions, and the untranslated regions of *CFHR5*. They reported 32 variants in *CFHR5* (including 28 rare and 4 common variants). Rare variants in *CFHR5* may further increase the genetic predisposition to IgAN, which indicates that *CFHR5* is a susceptibility gene for IgAN.

Table 2. Genome-wide association studies of acquired chronic kidney disease

Diseases	Sample size	Study population	Main findings	References
IMN	556 patients and 2388 controls	European	Two loci, *PLA2R1* and *HLA-DQA1*, strongly associated with IMN risk	[36]
IMN	1112 patients and 1020 controls	Chinese	The interaction between *PLA2R1* and *HLA-DQA1* variants contribute to the presence of anti-PLA2R antibodies	[37]
IMN	149 patients and 100 controls	Chinese	HLA-DRB1*15:01 and HLA-DRB3*02:02 alleles independently and strongly associate with PLA2R-related IMN	[39]
IgAN	244 patients, 4,980 healthy individuals, 186 families	European	*HLA* locus contained the strongest common susceptibility alleles responsible for genetic predisposition to IgAN in the European population	[53]
IgAN	1,950 patients and 1,920 controls	Chinese and European	Deletions in *CFHR1* and *CFHR3* were related to a reduced risk of IgAN	[49]
IgAN	500 patients and 576 controls	Chinese	*CFHR5* is a susceptibility gene for IgAN	[51]
IgAN	20612 participants	European and East Asian	Identified 6 new risk loci: 2 new independent signals at *HLA-DQB1* and *DEFA*; plus 4 in *ITGAM-ITGAX, VAV3*, and *CARD9*	[46]
IgAN	8,313 patients and 19,680 controls	Han Chinese	The allelic frequencies of the variants within *ST6GAL1*, *ACCS*, and *DEFA* correlated with geographical variations in IgAN prevalence	[47]
IgAN	1000 IgAN cases and 1000 controls	Chinese	Genetic variations and gene expression levels of *TNFSF13* were related to the susceptibility and severity of IgAN among the Han population	[56]
DN	5,825 with diabetes and 46,061 without diabetes	European	SNPs in HS6ST1 and RAB38/CTSC exerted a genetic effect on albuminuria only in individuals with diabetes	[75]
DN	743 patients and 646 controls	European	Loci 11p15.4, near the *CARS* gene, and 13q33.3 encompassing an intergenic region between *MYO16* and *IRS2* genes, were susceptible to kidney disease in both type 1 and 2 diabetes	[76]
DN	3,652 patients	Finnish	rs4972593 on chromosome 2q31.1 was a sex-specific genetic variant related to ESRD in patients with type 1 diabetes	[77]
DN	406 patients and 214 controls	Chinese	rs2796498 might be associated with DN	[79]

IMN: idiopathic membranous nephropathy; IgAN: IgA nephropathy; DN: diabetic nephropathy; SNP: single-nucleotide polymorphism; ESRD: end-stage renal disease

Kiryluk *et al.*[46] performed a follow-up evaluation in 20,612 European and East Asian individuals. They identified 6 new risk loci: 2 new independent signals at *HLA-DQB1* and *DEFA*; plus 4 in *ITGAM-ITGAX* (encoding integrin subunits M and X), *VAV3*, and *CARD9* (encoding caspase recruitment domain family member 9). Li *et al.*[47] conducted a GWAS comprising 8,313 patients and 19,680 controls. They reported that the allelic frequencies of the variants within *ST6GAL1* (encoding ST6 beta-galactoside alpha-2,6-sialyltransferase 1), *ACCS* (encoding 1-aminocyclopropane-1-carboxylate synthase homolog), and *DEFA* correlated with geographical variations in IgAN prevalence. Milillo *et al.*[54] reported that a *SPRY2* mutation inhibited the mitogen-associated protein kinase/extracellular signal-related kinase pathway, which was associated with an autosomal dominant form of IgAN. Gale *et al.*[55] reported that a common variation in *C1GALT1* influenced galactose-deficient IgA1 levels in the population, which was independently associated with the risk of progressive IgAN. Finally, Zhong *et al.*[56] reported that genetic variations and gene expression levels of *TNFSF13* were related to the susceptibility and severity of IgAN among the Han population [Table 2].

Overall, these studies emphasize complex multilocus model for IgAN. Multiple rare variants participating in a common network can influence disease susceptibility. Future investigations might explore the development of combined biomarkers to generate a prognostic model which can usher into potential genomic biomarkers and drug targets for personalized therapy[58].

Apolipoprotein L1-related kidney disease

The incidence of ESRD varies substantially between African and European individuals[59].

Rare mutations in *MYH9* (encoding myosin heavy chain 9) can cause monogenic diseases with kidney involvement, referred to collectively as Epstein-Fechtner syndrome, and thus represent candidates for ESRD diagnosis. The locus associated with ESRD was narrowed down subsequently filtered to three functional sequence variants in the nearby apolipoprotein L1 (*APOL1*) gene[60,61]. Risk-associated variants of *APOL1* (G1 and G2) are strongly linked to human immunodeficiency virus (HIV) associated nephropathy, FSGS, and CKD progression among African individuals[62]. They are considered to display such high frequencies because of a selection event primarily attributed to providing protection from *Trypanosoma brucei rhodesiense*[63,64].

A large number of follow-up studies have been carried out following identification of *APOL1* variants, which represent a milestone in kidney disease genetics. In the African American Study of Kidney Disease and Hypertension, 58.1% of patients in the *APOL1* high-risk group were diagnosed with ESRD or had double the serum creatinine level. In contrast, only 36.6% of those in the *APOL1* low-risk group reached the primary outcome[65].

In the Chronic Renal Insufficiency Cohort study, patients from the *APOL1* high-risk group experienced a more rapid decline in eGFR and an increased risk of the composite renal outcome than Caucasians[65]. In recent years, the *APOL1*-related disease spectrum was extended to systemic lupus erythematosus-associated glomerulopathy[66], proteinuria[67], and HIV-associated nephropathy[68]; it was not, however, investigated among African individuals with IgAN[69]. Taken together, these data suggest that detection of *APOL1* variants may serve as a prognostic marker for CKD progression.

As an additional benefit, *APOL1* genotyping could improve safety and success of kidney transplantation and facilitate the match of kidney donors with receivers. Freedman *et al.*[70] reported a strong association between the risk-associated *APOL1* genotype of the kidney donor and renal allograft failure. However, the genotype of the allograft recipient does not seem to affect allograft survival[71]. These findings raise a critical issue: should kidneys from donors with an *APOL1* risk-associated genotype be used for transplantation[72]? To address this question, the new *APOL1* Long-term Kidney Transplantation Outcomes Network is set to perform a large multicenter cohort study and evaluate the risk exposed by *APOL1* genotyping to both donors and recipients.

DN

Diabetes-related complications represent one of the most severe public healthcare challenges worldwide, with great social and economic burden[73]. DN is a prominent complication of diabetes and DN, the primary cause of ESRD. Moreover, it is highly heritable, with an incidence of approximately 35% in type 1 diabetes[74]. Nevertheless, the identification of gene variants strongly associated with DN has been limited.

The onset of albuminuria is regarded as an early landmark of DN progression. By performing meta-analyses of GAWSs and subsequent validation in diabetic and nondiabetic populations, Teumer *et al.*[75] identified associations between variants of cubilin-encoding *CUBN* and albuminuria in the overall population, whereas SNPs in *HS6ST1* and *RAB38/CTSC* exerted a genetic effect on albuminuria only in individuals with diabetes. Pezzolesi *et al.*[76] performed a trans-ethnic meta-analysis of data from the Japanese and Genetics of Kidneys in Diabetes collections. They reported that loci 11p15.4, near the cysteinyl-tRNA synthetase (*CARS*) gene, and 13q33.3 encompassing an intergenic region between the myosin XVI (*MYO16*) and insulin receptor substrate 2 (*IRS2*) genes, were susceptible to kidney disease in both type 1 and 2 diabetes. Sandholm *et al.*[77] performed a GWAS in 3,652 patients from the Finnish Diabetic Nephropathy (FinnDiane) study. They suggested that rs4972593 on chromosome 2q31.1 was a sex-specific genetic variant related to ESRD in patients with type 1 diabetes and may provide sex-specific protection against ESRD. A variant of *SCAF8*, encoding SR-related CTD associated factor 8, was consistently associated with type 2 DN in

different populations[78]. Genotyping of 406 type 2 diabetes patients and 214 controls from the Chinese Han population by Li *et al.*[79] revealed rs10789038 and rs2796498 polymorphisms in adenosine monophosphate-activated protein kinase subunit alpha 2 (*PRKAA2*), which were related to susceptibility to type 2 diabetes, whereas rs2796498 might be associated with DN [Table 2].

However, a large, comprehensive meta-GWAS effort was unable to identify clear loci associated with DN and many of the previously identified candidate signals were not validated[74]. Such apparent lack of reproducibility may be explained by differences in study design, populations, outcome ascertainment, and/or false-positive results between different studies[80]. Overall, these results indicate that the genetic landscape of DN is more complex than expected. An increasing number of large, diverse population-based studies on DN are required to provide conclusive genomic evidence.

TOWARDS PERSONALIZED MEDICINE: FUTURE PROSPECTS AND CHALLENGES

Personalized genomic medicine promises to combine genomic data with clinical phenotypes to develop novel clinical biomarkers for predicting CKD risk, drug selection, and for accurate monitoring of patient prognosis. To achieve this goal, numerous obstacles must be overcome, including determination of the most significant genetic markers, limiting the off-target effects of gene-based therapies, and conducting clinical studies to confirm genetic variants associated with drug response[7].

Questions regarding personalized medicine have been summarized by Joyner and Paneth[81]. One of the most important issues regarding what types of studies should be performed for personalized medicine because convenient samples have often been used without considering how selection bias and other factors could influence the outcome[81]. The Secretary's Advisory Committee on Genetic Testing had proposed four criteria to guide the assessment of benefits and risks with a genetic test: (1) analytical validity; (2) clinical validity; (3) clinical utility; and (4) social consequences. Strategies complying with these recommendations are required to obtain a panel of genomic biomarkers for diagnosis, prognostic evaluation, and genotype-guided counseling[82].

Even though mRNA expression levels are not necessarily a functional read-out, we previously reported that urinary podocalyxin, CD2-associated protein, α-actin4, and podocin mRNAs correlated with serum creatinine in DN patients[83]. Using targeted microarrays, we identified urinary vimentin mRNA as a biomarker to predict renal fibrosis and verified its predictive ability in CKD patients[84]. Upon iterative random forest analysis of a targeted microarray, four fibrosis-associated mRNAs (tumor growth factor β1, matrix metallopeptidase 9, tissue inhibitor of metalloproteinases 2, and vimentin) in urinary sediments were identified as sensitive predictors of tubulointerstitial fibrosis[85].

Despite compelling examples of the use of genomics to support personalized medicine, genomics alone is unlikely to provide sufficient information regarding disease pathophysiology and prognosis. Indeed, in spite of other omics approaches, including transcriptomics and metabolomics, have emerged as powerful tools for developing novel biomarkers for CKD in recent years[86-88], and proteomics remains the classic realm for biomarker discovery. In this respect, transcriptional, translational, and post-translational modifications, which cause functional changes to proteins and their function, represent another unexplored area. To maximize the information obtained by these various approaches, integrative personal omics profiling (iPOP) is increasingly regarded as a promising strategy that combines genomic, transcriptomic, proteomic (including autoantibodies), and metabolomic profiles from the same individual for long-term follow-up of their genomic/transcriptomic composition[89]. Longitudinal iPOP is extremely powerful in interpreting healthy and diseased states as it associates genomic information with other dynamic omics activity.

CONCLUSION

To date, there exist numerous potential genomic biomarkers of inherited and acquired CKD. Some of them have been utilized in clinical practice to improve diagnostic efficiency and to predict the response to immunosuppressive therapy as well as long-term outcomes of CKD patients. However, personalized medicine does not immediately provide a permanent solution for patient management. Further refinements in the application of personalized medicine are required to focus on genomics and other omics. Meticulous, large, multicenter, and cost-effective genomic studies are required to validate the potential candidates indicated herein, and novel genomic biomarkers for CKD are awaiting identification.

DECLARATIONS

Authors' contributions

Conceived the review: Cao JY, Liu BC
Wrote the paper: Cao JY, Zhou LT
Edited and revised manuscript: Cao JY, Zhou LT, Liu BC
Approved final version of manuscript: Liu BC

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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