

# Developments in renal pharmacogenomics and applications in chronic kidney disease

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**Abstract:** Chronic kidney disease (CKD) has shown an increasing prevalence in the last century. CKD encompasses a poor prognosis related to a remarkable number of comorbidities, and many patients suffer from this disease progression. Once the factors linked with CKD evolution are distinguished, it will be possible to provide and enhance a more intensive treatment to high-risk patients. In this review, we focus on the emerging markers that might be predictive or related to CKD progression physiopathology as well as those related to a different pattern of response to treatment, such as inhibitors of the renin–angiotensin system (including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers; the vitamin D receptor agonist; salt sensitivity hypertension; and progressive kidney-disease markers with identified genetic polymorphisms). Candidate-gene association studies and genome-wide association studies have analyzed the genetic basis for common renal diseases, including CKD and related factors such as diabetes and hypertension. This review will, in brief, consider genotype-based pharmacotherapy, risk prediction, drug target recognition, and personalized treatments, and will mainly focus on findings in CKD patients. An improved understanding will smooth the progress of switching from classical clinical medicine to gene-based medicine.

**Keywords:** angiotensin-converting enzyme, diabetes, hypertension, renal treatment, gene polymorphisms, biomarkers

## Natural history and epidemiology of chronic kidney disease (CKD)

CKD is defined as a reduced glomerular filtration rate (GFR), increased urinary albumin excretion, or both, and is a growing public health issue.<sup>1</sup> CKD progression is related to the GFR slope or key markers of renal damage (proteinuria or albuminuria) in diabetic patients. The Kidney Disease Outcome Quality Initiative defined CKD as the presence of renal impairment with a glomerular filtration rate (GFR) <60 mL/min.<sup>2</sup>

The kidney is a key organ in the urinary system, acting as a filter of the blood, with homeostatic functions such as the regulation of electrolytes, control of blood pressure (BP), and maintenance of acid–base balance. It also modulates water imbalance, the reabsorption of several substances (such as glucose, water, and amino acids), and the excretion of urea and ammonium. Important hormones, calcitriol, erythropoietin, and the enzyme renin, are also synthesized by the kidney. In summary, kidney damage can contribute to disturbances in the equilibrium between exogenous and endogenous elements including drugs and metabolites.

CKD includes different types of renal disease. Glomerular disease is the main group, consisting of diabetic and hypertensive nephropathies, which are the leading causes of

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CKD in developed countries.<sup>3</sup> Other groups of CKD, such as glomerulonephritis and CKD of unknown causes (CKDU), are more common in countries in Asia and sub-Saharan Africa, and account for 10% of CKD worldwide and 16% in India.<sup>4</sup> Differences between countries are related mainly to chronic lifestyle-related diseases, decreased birth rates, and increased life expectancy in the developed regions. By contrast, infectious diseases continue to be prevalent in low-income countries, secondary to poor sanitation, inadequate supply of safe water, and high concentrations of disease-transmitting vectors.

There are many published studies focused on traditional risk-initiating factors such as ethnicity, sex, age, hyperfiltration, diabetes mellitus, familiar history of CKD, metabolic syndrome, albumin excretion, cardiovascular disease, primary kidney disease, and urological disorders. Progression factors such as BP, smoking, uric acid, nephrotoxins, anemia, hypertension, dyslipidemia, obesity, cardiovascular disease, proteinuria, inflammation, and hemostasis have also been evaluated.<sup>5</sup>

Aside from the conventional factors, new markers have also been implicated in CKD pathogenesis and progression; these new markers include: adiponectin, kidney injury molecule-1, liver-type fatty acid binding protein, N-terminal pro-brain natriuretic peptide, factors involved in calcium–phosphate metabolism, A-type natriuretic peptide, adrenomedullin, neutrophil gelatinase-associated lipocalin, apolipoprotein A-IV, asymmetric dimethylarginine, and some recently identified genetic polymorphisms.<sup>5</sup>

Prevalence of CKD is estimated to be 5%–16% worldwide.<sup>6,7</sup> Complications include increased all-cause and cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anemia, mineral and bone disorders, and fractures.<sup>8–10</sup> The Epidemiology of Chronic Kidney Disease in Spain study estimated that approximately 10% of the Spanish adult population had some degree of CKD, and similar values were also estimated from other epidemiological studies.<sup>11,12</sup> CKD is reasonably prevalent,<sup>13</sup> symptoms do not appear until they are at an advanced stage, and progress occurs over several years, leading to end-stage renal disease (esrD).<sup>13</sup> In this sense, early screening of CKD would be useful to facilitate diagnosis.

The incidence of esrD differs extensively worldwide: 400 per million population per year in Taiwan; 300 per million population per year in USA and Mexico, and 100–150 per million population per year in Europe.<sup>14</sup> Depending on the country, there are several markers and risk factors for the progression of CKD. The increasing prevalence of

CKD generates concern about the cost of treatment for esrD. Bochud et al<sup>15</sup> describe that, despite the fact that prevalence of esrD is only about 0.2%, esrD programs now account for 6.7% of total medicare expenditure, and medicare costs associated with esrD increased by 57% between 1999 and 2004.

Considering the increasing prevalence and economic impact of CKD in previous decades, genetic studies have also been used to define the gene phenotypes involved in renal impairment, such as those related to high serum creatinine levels and GFR, hypertension, diabetic nephropathy, focal segmental glomerulosclerosis, albuminuria, and esrD.<sup>17</sup>

## Management issues in the treatment of CKD – clinical utility of pharmacogenomics

Here we review the link between CKD evolution and treatment, and we also identify the emerging markers and their pharmacogenomics.

### Management in the treatment of CKD

The incidence of CKD, as a serious public health disease with a high morbidity and mortality, is increasing. Proteinuria is a predictor of outcome, but genetic factors have also been related to the progression of renal disease. CKD management remains a clinical challenge.

In fact, the renin–angiotensin–aldosterone system (RAAS) is a major pathway involved in the pathogenesis and progression of diabetic nephropathy,<sup>18</sup> and the blockade of RAAS, which improves urinary protein levels, has been proven to reduce the slope of GFR in nondiabetic experimental animals and humans compared with an intensified BP control.<sup>19,20</sup>

### Classical treatments

We focused on two CKD preventive and therapeutic drugs and a complicating factor in CKD that are of potential interest in kidney pharmacogenomic applications: RAAS, Vitamin D receptor (VDR) agonists and salt-sensitivity.

### RAAS inhibitors

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) under similar conditions of blood pressure improve the progression of esrD and reduce the proteinuria rate better than non-RAAS antihypertensive drugs.<sup>18,21,22</sup> Captopril was the first ACE inhibitor that is effective in slowing the progression of diabetic nephropathy.<sup>21</sup> Indeed, RAAS inhibitors are considered for use

in classical treatment for primary hypertension and involve two key approaches for CKD improvement, summarized by hemodynamic and antihypertensive changes as well as anti-inflammatory and antifibrotic properties. The main mechanism for both is the decrease of angiotensin II levels. With regard to inflammation, angiotensin II induces lymphocyte proliferation by nuclear factor- $\beta$  (NF- $\kappa$  $\beta$ ) activation.<sup>23</sup> Fibrosis is attenuated by induction of extracellular-matrix proteins via transforming growth factor- $\beta$ .<sup>24</sup> On the other hand, hemodynamic beneficial effects are based on the maintenance of glomerular capillary hypertension by RAAS inhibitors.<sup>25</sup>

### VDR agonists

Several metabolic disturbances of CKD, such as acidosis, dyslipidemia, and vitamin D deficiency, could also be therapeutic targets for modifying the morbidity and mortality of CKD.<sup>26</sup>

Patients with esrD show a deficiency of 1,25(OH)2D3 vitamin D and, consequently, often undergo vitamin D therapy.<sup>27</sup> In fact, this therapy has been beneficial in hemodialysis patients in terms of survival.<sup>28</sup> In this sense, the analogue of vitamin D has been shown to attenuate kidney interstitial fibrosis<sup>29</sup> and ameliorate glomerulosclerosis.<sup>30</sup> Analogues of vitamin D have also been related to a decrease in albuminuria or proteinuria in CKD.<sup>31,32</sup>

The beneficial effects of 1,25(OH)2D3 on BP and CKD progression are mediated by the NF- $\kappa$  $\beta$  pathway<sup>33</sup> and by direct inhibition of 1,25(OH)2D3 on the RAAS.<sup>34,35</sup> Both NF- $\kappa$  $\beta$  and RAAS are involved in immune response and related inflammation, oxidative stress, and fibrogenesis.<sup>33,36</sup> Also, the prevention of secondary hyperparathyroidism by vitamin D treatment can ameliorate BP control.<sup>37</sup>

### Salt sensitivity

Salt sensitivity of BP is still not well defined. It is accepted that a person could be considered salt-sensitive when BP increases by 5%–10% after a large increase in dietary salt intake.<sup>38</sup> It has been described that dietary sodium intake have an impact on the efficacy of RAAS blockers in preventing CKD and cardiovascular disease.<sup>39</sup> On the other hand, RAAS blockers' antiproteinuric effect is impaired in patients with high sodium intake. An observational trial described that increasing sodium intake was associated with a linear increase in the risk of progression of esrD.<sup>40</sup>

### Novel therapeutic approaches

Drugs focused on targeting inflammation and damaged systems (fibrosis, endothelin, oxidation, and advanced

glycation end products) could be beneficial in preventing CKD progression.<sup>41</sup>

Bardoxolone methyl and palmitoylethanolamide are new drugs for the treatment of CKD that target inflammation. Bardoxolone methyl, a first-in-class oral nuclear factor erythroid 2-related factor 2 agonist, seemed to have potential as a drug for improving renal function in advance diabetic nephropathy patients in a Phase II trial. However, in the Phase III study, the treatment had to be stopped due to emerging toxicity.<sup>42,43</sup>

On the other hand, palmitoylethanolamide belongs to a fatty acid ethanolamine family, and is a new and safe nonsteroidal, anti-inflammatory, and antifibrotic agent for CKD<sup>44,45</sup> with activity at the peroxisome proliferator-activated receptor alpha.<sup>46–48</sup>

## Clinical utility of pharmacogenomics

There are numerous reasons to address the pharmacogenomics that are related to different kidney functions and treatments. Drug-treatment benefits in the pharmacogenomics of patients with kidney disease are based on avoiding nephrotoxic drugs, personalizing antihypertensive and cardiovascular drugs, and identifying the enzymes and proteins involved in the pharmacokinetics of drugs to improve renal function and BP.<sup>15</sup> Therefore, renal pharmacogenomics encompasses three important issues: ACE inhibitors, VDR agonists, and dietary salt intake.

Forty-four genes are included in the Pharmacogenomics Knowledge Database as very important pharmacogenes for their effects on renal function and diseases.<sup>15</sup> The most important genes involved in CKD disease are: CYP1A2 and CYP3A5; ABCB1; and methylenetetrahydrofolate reductase.

### Phase I enzymes (CYP1A2 and CYP3A5)

The large interindividual variability in drug response is heritable,<sup>49,50</sup> and single-nucleotide polymorphisms (SNPs) in genes encoding drug-metabolizing enzymes are involved in CKD.

CKDU constitutes 10% of CKD, and no specific causative agents have been identified. However, environmental toxins and heavy metals may be involved,<sup>51,52</sup> such as persistent organic compounds that include polychlorinated biphenyls, organochlorine pesticides, and dioxins. Organic toxins are detoxified by cytochrome P450 enzymes being the CYP1A1, the enzyme that is most involved in the metabolism of persistent organic compounds. Several authors have reported the association of CYP1A1 polymorphism with various

diseases such as diabetes<sup>53</sup> and neoplasia.<sup>54–56</sup> The prevalence of homozygous CYP1A1\*2A mutants ranges between 2% and 18%, and for the heterozygous TC ranges between 32% and 55%. Siddarth et al performed a case-control study to evaluate the association of CYP1A1 in patients with CKD, and observed that subjects carrying at least one mutant allele of CYP1A1\*2A (TC, CC) and \*2C (AG, GG) had a 1.4- to twofold increased risk of CKDU as compared to those with the wild-type homozygous genotype, ie, TT (\*2A) and AA (\*2C).<sup>57</sup> However, other studies on Indian populations observed inter- and intra-ethnic variations of these two polymorphisms.<sup>58–60</sup>

### CYP1A2

CYP1A2 enzyme is responsible for 13% of the cytochrome P450 activity and has a large number of endogenous and exogenous substrates. There is a great amount of interindividual and inter-ethnic CYP1A2 variability due to both environmental and genetic factors. However, the mechanism of association between CYP1A2 and CKD is unknown, but probable mechanisms include an action mediated by CYP1A2 substrates.

Compared to other CYP-family genes, there is little data on CYP1A2 pharmacogenomics and antihypertensive drugs. The main attention has been focused on antipsychotic drugs, theophylline, and melatonin.<sup>61</sup> Antihypertensive-drug studies have been conducted with CYP2C9, which metabolizes different antihypertensive angiotensin II receptor antagonists, such as losartan, irbesartan, candesartan, and valsartan. CYP2C9 genotype has been shown to influence losartan metabolism, and response to irbesartan differed depending on CYP2C9 genotype.<sup>62</sup>

Nutrigenomic studies have been performed to provide a mechanistic hypotheses for the relationship between CYP1A2 and BP. An increased risk of myocardial infarction with increased coffee consumption was reported among carriers of the CYP1A2 C variant.<sup>63</sup> Regular coffee or caffeine intake increases BP,<sup>64</sup> but there is a tolerance to the acute cardiovascular effects. There is no clear evidence that regular caffeine intake in the long-term increases the incidence of hypertension in the CYP1A2 carriers.<sup>65,66</sup>

### CYP3A5

There are a large interindividual and inter-ethnic variations in CYP3A5\*1 allele frequency. The CYP3A5 gene is associated with BP control, but further studies are needed to confirm the relationship with salt sensitivity in humans.<sup>67</sup> One hypothesized mechanism is the conversion of cortisol

into 6 beta-hydroxycortisol, by CYP3A5, in the kidney. However, results are not conclusive. It would be of major interest to also clarify the putative role of CYP3A5 activity on intestinal drug disposition following various dietary salt intake levels.

CYP3A4 and CYP3A5 show similar substrate specificity for each of amlodipine, felodipine, nifedipine, atorvastatin, pravastatin, cerivastatin, lovastatin, celiprolol, digoxin, diltiazem, enalapril, losartan, and verapamil.<sup>68,69</sup> However, the majority of pharmacogenetic studies are concentrated on tacrolimus and cyclosporine as CYP3A5 genotypes clearly influence the pharmacokinetics of the immunosuppressant tacrolimus.<sup>70</sup> Only a few studies with small sample sizes have analyzed the role of CYP3A5 variants on the response to drugs used to treat cardiovascular conditions. CYP3A5 variants appear to influence the pharmacokinetics of statins,<sup>71</sup> and CYP3A5\*1 carriers may experience a diminished pharmacological effect of verapamil.<sup>72</sup> Eap et al studied the combined action of CYP3A5 and ABCB1 variants on BP, and observed that there was an association with altered response to lisinopril.<sup>73</sup> A study of plasma amlodipine concentrations in 40 healthy Korean men observed that carriers of the CYP3A5\*3/\*3 genotype had lower levels of amlodipine than CYP3A5\*1 carriers, but the BP decrease was similar in both groups.<sup>74</sup>

### Transporters (ABCB1)

The ABCB1 gene encodes the P-glycoprotein (also named as Pgp, MDR1, and ABCB1), which belongs to the superfamily of human ABC transporters. It is also known as the multidrug resistance gene, and several ABCB1 genetic variants have been shown to influence Pgp expression in humans, including the 3435 C>T and 2677 G>T variants. Pgp is an efflux pump that transports endogenous substrates (eg, steroids, lipids, phospholipids, and cytokines), drugs (eg, digoxin, cyclosporine, tacrolimus, diltiazem, verapamil, etc), and other exogenous substrates out of the cells.<sup>75</sup> ABCB1 polymorphisms have been widely studied in transplant patients treated with cyclosporine, and it was observed that TT carrier patients on C3435T, G2677T, and C1236T SNPs (Pgp-low pumpers) showed lower Pgp activity than noncarriers.<sup>76</sup>

SNPs related to drug transporters have also been described in CKD patients. The C3435T SNP in the gene of ABCB1 that codify P-glycoprotein was correlated with renal function and BP in two Chinese populations.<sup>77</sup> Patients with TT genotype showed an increased risk of CKD, and higher systolic BP and pulse pressure. Results were similar in elderly



subjects, with CKD with a higher risk of CKD progression and hypertension. These authors concluded the importance of ABCB1 SNP in CKD specially in elderly population. The regulation of Pgp expression seems to be influenced by multiple nuclear receptors: namely, constitutive androstane receptor-beta<sup>78</sup> and VDR.<sup>79–81</sup>

Although the role of ABCB1 genes are widely known in the field of transplant patients, the application in CKD progression and BP regulation is still not well defined.

### Nuclear receptors (VDR and PXR)

VDR is widely expressed in the human kidney, namely in the epithelial cells of the proximal and distal tubules, collecting duct, and glomerulus.<sup>82</sup> VDR is a ligand-induced nuclear receptor that regulates the expression of over 900 genes throughout the genome,<sup>83,84</sup> such as ABCB1,<sup>79–81</sup> CYP24A1,<sup>84</sup> CYP3A4,<sup>85</sup> CYP3A7, FGF23,<sup>86</sup> and SLC34A3. Most studies have attempted to correlate VDR polymorphisms with the development of secondary hyperparathyroidism.<sup>87</sup> Grzegorzewska and Ostromecki described the distribution of variants of vitamin D-binding protein gene, VDR with respect to PTH serum concentrations, and response to cinacalcet treatment in patients with secondary hyperparathyroidism.<sup>88</sup> Other studies have investigated the association of polymorphisms in the VDR gene with protection against esrD and periodontitis.<sup>89</sup>

Variants of *VDR* and variants within the *VDR* gene may influence renal function and BP, but there is a lack of conclusive data on the association with renal function. In a study of people of Indian and African descent, vitamin D deficiency was significantly associated with increased diastolic BP and triglyceride levels, and reduced high-density lipoprotein cholesterol.<sup>90</sup> There is evidence of associations between *VDR* variants and diabetes, which is a major CKD risk factor. Randomized controlled trials have provided convincing evidence that VDR agonists confer renoprotection in humans.<sup>91–94</sup>

Although *PXR* is not currently considered to be a gene associated with BP or renal function, its role in controlling the expression of genes such as ABCB1 and CYP3A5, its involvement in steroid hormone metabolism, its action on lipid and energy metabolism, its action on inflammation, as well as its interaction with VDR all point toward PXR being an important player in kidney diseases. The role of PXR as a xenobiotic and endobiotic sensor, its ability to bind to a large array of ligands, and its numerous transcriptional gene targets suggest that PXR may mediate complex gene–environment, drug–environment and drug–drug interactions with important consequences on human health, including kidney function.

### ACE gene

The ACE gene encodes ACE, an enzyme involved in the RAAS and which plays a key role in BP control. There is a high interindividual variability in circulating ACE levels, with the 287-bp Alu-repeat sequence insertion/deletion polymorphism located in intron 16 (ACE I/D) being the most extensively studied ACE genetic variant, with more than 4,000 publications during the past 20 years.<sup>95</sup> Other ACE variants have been described, and the genetic diversity of ACE is particularly high in people of African descent.<sup>96–98</sup> The associations of the ACE I/D polymorphism with hypertension and cardiovascular disease have been inconsistent. Some authors suggest that testing for the ACE I/D polymorphism is useful for predicting the renoprotective effect of ACE inhibitor or angiotensin-receptor blocker treatment in patients with kidney disease.<sup>99</sup> There is currently no evidence to support a role of the ACE I/D polymorphism in predicting future risk of cardiovascular events or BP response to ACE inhibitors in the absence of renal dysfunction.

One of the first pharmacogenetic studies evaluating efficacy variability of ACE inhibitors on albumin excretion rates in nonhypertensive insulin-dependent patients with normoalbuminuria or microalbuminuria was conducted in 1998.<sup>101</sup> The application of ACE polymorphisms has been confirmed by different authors.<sup>100</sup> Patients carrying the II genotype had a higher albuminuria reduction and better BP control.<sup>101,102</sup> In type I diabetic patients, the I allele had the best outcomes in terms of renal phenotypes (with decline in albuminuria and decreased BP),<sup>103–105</sup> and type 2 diabetic patients with the II genotype plus ID alleles had decreased mortality, esrD, and diabetes progression.<sup>106</sup> However, conflicting data exist as some other authors did not find a correlation between BP and ACE variants.<sup>107–109</sup> ARB-treatment outcomes have also been evaluated in different studies, and the data shows that DD genotype carriers have diminished renoprotection.<sup>105,110</sup> A recent meta-regression analysis evaluated 129 papers to study the effect of ACE I/D polymorphisms on CKD risk and concluded that the D allele had the highest risk for CKD in hypertensive Asian males (odds ratio, 3.75).

## Review of pathogenesis: specific genetic polymorphisms in CKD Pathogenesis

CKD is a complex pathophysiologic process resulting from multiple etiologies. It is classified as a multifactorial disease secondary to a combination of genetic and environmental

factors that influence the onset and development of esrD.<sup>111</sup> Risk factors for development of CKD could be gathered in two groups: susceptibility to kidney disease due to sociodemographic and genetic factors; and exposure to variables that can initiate kidney disease.

The main risk factors for CKD described in the literature include hypertension, obesity, and diabetes. The global prevalence of hypertension in adults was estimated to be about 26% (972 million cases) in 2000.<sup>112</sup> Prevalence of hypertension is higher in urban populations than in rural populations in developing countries (global prevalence is 639 million [66%]).<sup>113</sup> The worldwide prevalence, adjusted for age and sex, is projected to increase to 1.56 billion by 2025. Therefore, treatment of hypertension is one of the most important interventions in the pharmacological management of CKD. Similar trends are apparent for diabetes and obesity.<sup>114,115</sup> The worldwide prevalence of diabetes in adults is estimated to be 6.4%, affecting 285 million people, and is expected to rise to 7.7% by 2030 (439 million cases). The increase in overweight and obese children is particularly alarming.<sup>114</sup> Obesity raises BP physical compression of the kidneys by increasing renal tubular sodium reabsorption, impairing pressure natriuresis, and by activating the sympathetic nervous system and RAAS.<sup>116</sup>

Genetic susceptibility is an important determining factor for the onset and/or progression of esrD and its complications, and different studies have identified new susceptibility loci for reduced renal function.<sup>117</sup> Although environmental risk factors and interactions between genes and environment undoubtedly play an additional role, nontraditional risk factors such as oxidative stress, inflammation, and immune processes may be important contributors to the pathogenesis and progression to esrD.

## Polymorphisms in CKD pathogenesis

Here we present genetic polymorphisms related to CKD and the progression to esrD (Table 1).

Inflammation could be a causal factor in the development of CKD and may be established before the onset of renal disease. The inflammatory response involved in renal damage produces proinflammatory cytokines and chemokines, an increase of leukocytes, intensification of interstitial nephritis, and a progression of fibrosis. Recent studies have suggested roles for toll-like receptor 9 (TLR-9) in the development of renal diseases such as glomerulonephritis,<sup>118</sup> lupus nephritis,<sup>119</sup> and the progression of immunoglobulin A nephropathy, and have also suggested that TLR-9 could be associated with severe

clinical phenotypes.<sup>120,121</sup> A case-control study observed significantly different allelic distribution of 1237T/C, but not 1486T/C or 1635G/A, between esrD patients and controls. Higher GFR values for patients with the TLR-9-1237TT genotype were obtained, but differences were not statistically significant.<sup>122</sup>

Associations of 48 chemokine gene variants with esrD have been tested; however, the small sample size did not allow to detect moderate effects. The authors found association between esrD and four SNPs.<sup>123</sup> Two of them expressed protection (interleukin 4 receptor A/G and CCL2) and the other two expressed susceptibility (STAT4 binding site and nitric oxide synthase 3). However, after adjusting for multiple testing, the results were not significant. Singh et al found a significant association between a high risk for esrD and both CXCL2G801A and CXCR2, whereas CCL2I/D showed a reduced risk for esrD.<sup>124</sup> In the process of CKD progression to the terminal stage, the cytokine-mediating angiotensin action (transforming growth factor- $\beta$ 1) could be also related as it is involved in the process of tissue sclerosis. With regard to that, Nabrdalik et al performed a case-control study and identified the mutant C allele as the related allele with the higher risk of CKD (twofold elevated risk).<sup>125</sup> These results were similar to those observed by Buraczynska et al and Coll et al.<sup>126,127</sup> In contrast, other authors did not find an association between transforming growth factor- $\beta$ 1 and CKD occurrence.<sup>128–130</sup>

Hypertension is second to diabetes as the leading independent cause of esrD. There is available evidence supporting the association of genetic variants of the RAAS and pharmacogenetic responses. ACE gene polymorphism (ACE-ID) has been associated with higher circulating plasma ACE concentrations,<sup>131</sup> and the molecular variant M235T of the AGT gene has been associated with higher plasma AGT levels in patients homozygous for the T allele.<sup>132</sup> Polymorphisms related to treatment efficacy with ACE inhibitors and angiotensin II receptor blockers (ARBs) are explained in Table 1. Several studies have linked variants of AGTR1 with hypertension and heart diseases, but conclusive data related to esrD is lacking. The reduction of BP by ACE inhibitors is mediated by decreased formation of the vasoconstrictor angiotensin II, and by increased levels of the vasodilator bradykinin and endothelial nitric oxide synthase (eNOS). Bradykinin receptor B2 and eNos gene polymorphism could affect the response to ACE inhibitors, and was studied by Silva et al.<sup>133</sup> The results showed that the C allele for eNOS and TT genotype for the bradykinin receptor B2 were more frequent in good responders.

**Table 1** Characteristics and results of the main published studies involving gene polymorphisms and effect on renal function

Study	Population	N	Variable studied	SNPs	rs	Effect
Siddarth et al <sup>127</sup>	North Indian	334 cases (CKD patients), 334 controls (healthy patients)	Occurrence of CKD	CYP1A1*2A	rs4646903	C allele was associated with risk of CKD. TC OR =1.54 (P=0.013) and CC OR =2 (P=0.003)
Kao et al <sup>137</sup>	African-American	1,372 cases (ESRD patients), 806 controls	Occurrence of CKD	CYP1A1*2C	rs1048943	G allele was associated with risk of CKD. AG OR =1.67 (P=0.002) and GG OR =2.24 (P=0.004)
				MYH9	rs2032487	Diabetic patients: no association was observed Nondiabetic patients: C allele was associated with increased risk of ESRD (C OR =2.41, P=2.78×10 <sup>-9</sup> ) Hypertensive patients: C allele was associated with increased risk of hypertensive ESRD (C OR =2.28, P=5.77×10 <sup>-7</sup> ) FSGS patients: C allele was associated with increased risk of FSGS ESRD (C OR =4.85, P=6.14×10 <sup>-5</sup> ) Diabetic: no association was observed Nondiabetic patients: A allele was associated with increased risk of ESRD (A OR =3.03, P=1.47×10 <sup>-7</sup> ) Hypertensive patients: A allele was associated with increased risk of hypertensive ESRD (A OR =2.6, P=5.98×10 <sup>-5</sup> ) FSGS patients: A allele was associated with increased risk of FSGS ESRD (A OR =5.38, P=8.07×10 <sup>-7</sup> ) Diabetic patients: no association was observed Nondiabetic patients: C allele was associated with increased risk of ESRD (C OR =1.58, P=1×10 <sup>-3</sup> ) Hypertensive patients: C allele was associated with increased risk of hypertensive ESRD (C OR =1.69, P=3.36×10 <sup>-3</sup> ) FSGS patients: no association was observed Diabetic patients: no association was observed Nondiabetic patients: T allele was associated with increased risk of ESRD (T OR =1.71, P=3.21×10 <sup>-5</sup> ) Hypertensive patients: T allele was associated with increased risk of hypertensive ESRD (T OR =1.62, P=2.04×10 <sup>-3</sup> ) FSGS patients: T allele was associated with increased risk of FSGS ESRD (T OR =2.81, P=1.19×10 <sup>-3</sup> ) Diabetic patients: no association was observed Nondiabetic patients: C allele was associated with increased risk of ESRD (C OR =2.40, P=2.8×10 <sup>-8</sup> ) Hypertensive patients: C allele was associated with increased risk of hypertensive ESRD (C OR =2.32, P=4.37×10 <sup>-7</sup> ) FSGS patients: C allele was associated with increased risk of FSGS ESRD (C OR =4.34, P=9.57×10 <sup>-5</sup> )
				MYH9	rs16996677	
					rs5756130	
					rs5756129	
					rs4821481	

(Continued)

Table 1 (Continued)

Study	Population	N	Variable studied	SNPs	rs	Effect
					rs3752462	Diabetic patients: no association was observed
						Nondiabetic patients: T allele was associated with increased risk of ESRD (T OR =2.11, $P=1.98 \times 10^{-5}$ )
						Hypertensive patients: no association was observed
					rs5756152	FSGS patients: T allele was associated with increased risk of FSGS ESRD (T OR =3.5, $P=2.53 \times 10^{-3}$ )
						Diabetic patients: no association was observed
						Nondiabetic patients: A allele was associated with increased risk of ESRD (A OR =2.59, $P=2.25 \times 10^{-6}$ )
					rs1005570	Hypertensive patients: A allele was associated with increased risk of hypertensive ESRD (A OR =2.54, $P=1.59 \times 10^{-5}$ )
						FSGS patients: A allele was associated with increased risk of FSGS ESRD (A OR =4.63, $P=2.44 \times 10^{-6}$ )
						Diabetic patients: no association was observed
					rs16996674	Nondiabetic patients: A allele was associated with increased risk of ESRD (A OR =2.56, $P=4.33 \times 10^{-9}$ )
						Hypertensive patients: A allele was associated with increased risk of hypertensive ESRD (A OR =2.07, $P=3.54 \times 10^{-5}$ )
						FSGS patients: A allele was associated with increased risk of FSGS ESRD (A OR =4.49, $P=3.63 \times 10^{-7}$ )
Matsha et al <sup>140</sup>	People of African ancestry	716 chosen from the general population	Renal function: estimated GFR calculated with the MDRD formula	MYH9	rs5756152	Diabetic patients: no association was observed
						Nondiabetic patients: T allele was associated with increased risk of ESRD (T OR =3.1, $P=4.14 \times 10^{-7}$ )
						Hypertensive patients: T allele was associated with increased risk of hypertensive ESRD (T OR =2.78, $P=3.56 \times 10^{-5}$ )
Tavira et al <sup>41</sup>	Spanish	592 chosen from the general population	Renal function: estimated GFR calculated with the MDRD formula	MYH9	rs3752462 T	FSGS patients: T allele was associated with increased risk of FSGS ESRD (T OR =6.84, $P=6.82 \times 10^{-9}$ )
						Diabetic patients: G allele was associated with increased renal function (+11 mL/min/1.73 m <sup>2</sup> , $P=0.0002$ )
						Nondiabetic patients: no association was observed
Cooke et al <sup>139</sup>	European American	536 cases (type 2 diabetes mellitus ESRD patients), 467 controls (type 2 diabetes mellitus patients), 960 controls (healthy patients)	Occurrence of type 2 diabetes mellitus ESRD	MYH9	rs4821480 T	No association was observed
						T allele was associated with GFR <60 mL/min/1.73 m <sup>2</sup> ( $P=0.003$ )
						G allele was more frequent in GFR < 60 mL/min/1.73 m <sup>2</sup> ( $P=0.16$ )
					rs4821480	Versus diabetic nonP: G allele had a trend of association with ESRD (OR =6.14, $P=0.053$ )
						Versus nondiabetic nonP: G allele had a trend of association with ESRD (OR =2.5, $P=0.107$ )
						Versus controls (diabetic and nondiabetic): G allele was associated with ESRD (OR =3.11, $P=0.033$ )



rs2032487								Versus diabetic nonP: G allele had a trend of association with ESRD (OR =6.09, P=0.054) Versus nondiabetic nonP: G allele had a trend of association with ESRD (OR =3.13, P=0.056) Versus controls (diabetic and nondiabetic): G allele was associated with ESRD (OR =3.72, P=0.017) Versus diabetic nonP: G allele had a trend of association with ESRD (OR =6.08, P=0.055) Versus nondiabetic nonP: G allele had a trend of association with ESRD (OR =3.11, P=0.058) Versus controls (diabetic and nondiabetic): G allele was associated with ESRD (OR =3.70, P=0.017) No statistical analysis due to the low frequency in European Americans
rs4281481								
rs375462		APOLI						
rs73885319		APOLI	Composite renal outcome: doubling of serum creatinine level from baseline or incident ESRD.					
rs60910145								
rs71785313								
rs5743836		TLR-9	Occurrence of ESRD	630 cases (ESRD patients), 415 controls (healthy patients)	Chinese			Diabetic patients: black patients in the APOLI high-risk and low-risk groups, compared with white patients, had an increased risk of composite renal outcome: OR =1.95, P<0.001 and OR =1.4, P=0.006, respectively. Nondiabetic patients: black patients in the APOLI high-risk and low-risk groups, compared with white patients, had an increased risk of composite renal outcome: OR =2.68, P<0.001 and OR =1.57, P=0.01, respectively C allele was associated with increased risk of ESRD (C OR =4.36, P=0.001) C allele was associated with reduced risk of ESRD (C OR =0.71, P=0.05) No association was observed
rs187084								
rs352140		IL4R	Occurrence of ESRD	276 cases (kidney transplant patients), 288 controls (healthy patients)	Spanish			AG genotype was associated with reduced risk of ESRD. (AG OR =0.66, P=0.025) A genotype was associated with increased risk of ESRD (A OR =1.82, P=0.0064) C genotype was associated with reduced risk of ESRD (C OR =0.7, P=0.0051) T genotype was associated with increased risk of ESRD (T OR =1.31, P=0.043)
rs1801275								
rs301640		STAT4 binding site						
rs4586		CCL2						
rs7830		NOS3						
rs1801157		CXCL12G801A	Development of ESRD	200 cases (ESRD patients), 200 controls (healthy patients)	North Indian			GA genotype was associated with ESRD risk (OR =1.55, P=0.039) CT genotype was associated with ESRD risk (OR =1.65, P=0.02)
rs1801032		CXCR2						

(Continued)

Table 1 (Continued)

Study	Population	N	Variable studied	SNPs	rs	Effect
Nabrdalik et al <sup>125</sup>	Caucasian	109 cases (CKD patients of at least stage 3), 111 controls (healthy patients)	Occurrence of CKD Progression of CKD: mean reduction of GFR per year (calculated with MDRD). Hypertension appearance	CCL1/D CCL2A518G TGFβ1	rs3917887 rs1024611 rs1800471	DD genotype showed a reduced risk of ESRD (OR =0.45, P=0.035) No association was observed Occurrence of CKD: C allele was related with higher risk of CKD (OR =2.0, P=0.035) Progression of CKD: no association was observed Hypertension occurrence: G genotype was associated with risk of hypertension (OR =5.9, P=0.0021)
Silva et al <sup>133</sup>	Brazilian	106 hypertensive patients treated with enalapril	Response to enalapril in hypertensive patients	eNOS BDKRB2		Good responders showed higher frequencies of the TC and CC genotypes TC OR =0.35, P=0.0005 and CC OR =0.38, P=0.0424 Poor responders showed higher frequencies of TT genotypes. TT OR =3.06, P=0.0106

**Notes:** G1 risk allele: presence of rs73885319 and rs60910145; G2 risk allele: presence of rs7178513 APOL1 risk: defined according to the number of copies of the risk alleles. Zero or one copy = low risk. Two copies = high risk.  
**Abbreviations:** APOL1, apolipoprotein L1; CKD, chronic kidney disease; eNOS, nitric oxide synthase; (endothelial) ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; nonP, non-nephropathy; OR, odds ratio; SNPs, single-nucleotide polymorphisms; TGFβ1, transforming growth factor beta 1; BDKRB2, bradykinin receptor B2; AASK, African American Study of Kidney Disease and Hypertension; CRIC, Chronic Renal Insufficiency Cohort.

The MYH9 gene encodes for the non-muscle myosin IIA heavy chain, a subunit of myosin IIA protein that is involved in several functions including cytokinesis, cell motility, maintenance of cell shape, and secretion. Recent studies have linked MYH9 SNPs/haplotypes to a risk of developing focal segmental glomerulosclerosis, hypertensive nephropathy, and nondiabetic esrD among African and Hispanic Americans.<sup>134–138</sup> Because African Americans seem to have greater risk than European Americans, even after considering socioeconomic status, a genome-wide admixture scan was performed to find genetic risk alleles. MYH9 genes were associated with two- to four-times greater risk of nondiabetic esrD. Multiple clusters of SNPs was performed and remained significant.<sup>137</sup> As African Americans showed a higher risk for specific forms of CKD, the influence of MYH9 SNPs was studied in African ancestry populations. In diabetic participants, the G allele of rs5756152 was associated with a significant decrease in serum creatinine and GFR, but not in nondiabetic patients. Interactions by diabetic status were also significant, but rs12107 analysis showed no association with renal function.<sup>140</sup>

In a Spanish cohort of healthy elderly individuals, Tavira et al studied the effect of common MYH9 SNPs on renal function. The multivariate analysis showed that age, diabetes, sex, and the MYH9 genotype were risk factors for GFR <60 mL/min/1.73 m<sup>2</sup>. MYH9 rs3752462 T carriers had lower mean GFR compared to CC homozygotes.<sup>141</sup> Aside from MYH9 polymorphisms, variations in the gene encoding apolipoprotein L1 (APOL1) have recently been shown to be associated with kidney disease in African Americans.<sup>142–145</sup> Fifteen MYH9 SPNs and two APOL1 SNPs were studied in association with type 2 diabetes mellitus in European Americans. As reported previously, MYH9 polymorphisms were associated with type 2 diabetes mellitus esrD susceptibility, and APOL1 could not be tested for as the frequency was not appreciable.<sup>139</sup> APOL1 variants have previously been studied and it was concluded that these polymorphisms were not present in European Americans or in Europeans.<sup>146</sup> Polymorphisms in APOL1 related with CKD progression has been evaluated in two populations: black African Americans with kidney disease and hypertension (African American Study of Kidney Disease and Hypertension); and black and white African and European Americans with chronic renal insufficiency (Chronic Renal Insufficiency Cohort study). Black subjects in the APOL1 high-risk group had a more rapid decline in GFR and a higher risk of composite

renal outcome, defined as doubling serum creatinine or incident of esrD, compared to white patients.

## Developments in pharmacogenomics – clinical implications and personalized therapies

In the last few decades, despite the fact that CKD diagnosis and progression risks are still based on clinical observations, there have been notable advances in genetic studies that have led to a more selective set of therapeutic strategies.<sup>147</sup> Herein, we review some of the potential applications of genotyping that have benefits for CKD risk prediction, guided treatment, and guided individualized strategies.

Nowadays, diagnosis and determination of risk factors based on genotyping is available for many disorders such as breast cancer (by testing BRCA 1 and 2).<sup>150</sup> However, in CKD patients, definitive DNA-based diagnostics and risk prediction have not yet been made available.<sup>17</sup>

However, recent studies in African-American patients of nondiabetic CKD have profiled possible risk factors in polymorphisms of apolipoprotein L-I genes<sup>136,144,145</sup> and of the non-muscle myosin heavy chain type II isoform A.<sup>136,137</sup>

The benefits derived from pharmacogenetics are aimed at individualizing treatments, reducing drug side effects, and improving drug efficacy. For example, the effects of polymorphism of genes in the cytochrome P450 enzyme complex are widely known, and genetic tests for this polymorphism before receiving treatments are routinely practiced.<sup>151,152</sup> Also, patients with stage 5 esrD undergoing hemodialysis may present allelic variants in the cytochrome P450 2D6 (CYP2D6), which would be determinant in the metabolism of codeine into morphine, thus pointing to different susceptibility to morphine.<sup>153</sup> Other therapeutic applications focusing on treatment with atenolol and enalapril have been identified involving polymorphism of ACE; the suggestion of these applications is that homozygous patients with a deletion allele may benefit from other antihypertensive drugs.<sup>154</sup> These novel applications in pharmacogenomics that involve personalized treatment of patients with CKD provide clinicians with key management tools that are far from classical treatments.

Studying genetic variants may be helpful for personalized therapeutic strategies. Those genetic variants that would allow prediction of risks relative to drug exposure could guide physicians in evaluating cost-effectiveness of new strategies in CKD patients. For example, deletion polymorphism in

the CC-chemokine receptor 5 (CCR5) gene (*CCR5Δ32*), which is known to cause a dysfunctional CCR5 protein, has been related to an improvement of inflammatory state with better survival.<sup>155,156</sup> Therefore, patients with esrD undergoing hemodialysis and, thus, suffering from a well-known persistent inflammatory state (ie, wasting syndrome) would potentially benefit from a blockade of CCR5 based therapy.<sup>18,157</sup> Glutathione S-transferase M1 (GST M1) null allele is another polymorphism related to CKD progression caused by deletion in the GST M1 gene and related to oxidative damage protection.<sup>158,159</sup> In fact, hemodialysis patients are exposed to a higher oxidative stress status, and it has been shown that hemodialysis patients homozygous for the *GST M1* null allele had higher risk for death compared with those who possess GST M1 activity.<sup>160</sup>

Interestingly, uremic milieu (which includes oxidative stress), wasting syndrome, inflammation, anemia, vascular calcification, and concerns associated with dialysis would render patients with CKD more susceptible to genetic variants.<sup>155,161–163</sup> Knowing these interactions of the gene environment could be helpful in clinical practice in addressing patients' nutritional habits and lifestyle.<sup>164</sup> In fact, renal-function impairment per se has been considered an environment factor, varying the effect of two polymorphisms of RAS (AGTR1 A1166C and ACE insertion/deletion) on left ventricular hypertrophy.<sup>165–170</sup> Another example of gene–environment interaction that has been established is in the susceptibility of some patients to respond to ACE inhibitors depending on dietary sodium intake and the ACE deletion/deletion genotype, which would encourage the prescription of a salt-restricted diet in those patients with this genotype variant.<sup>171</sup>

It has been questioned whether epigenetics is involved in esrD progression.<sup>172</sup> In fact, inflammation, atherosclerotic processes, and aging are related to DNA methylation and act as catalyzers in the poor prognosis of the cardiovascular disease in dialysis patients.<sup>155,161,172,173</sup> These findings highlight the importance of targeting the epigenome with epigenetic drugs. Therapeutic applications of epigenetics in patients with CKD, and even in patients with esrD, could be focused on RNA interference, which is crucial in renal homeostasis, mainly linked to podocyte dedifferentiation-related proteinuria.<sup>174–177</sup> Hyperhomocysteinemia has been described in CKD and esrD patients.<sup>173,178</sup> These patients showed high levels of S-adenosylhomocysteine, causing hypomethylation of DNA.

Thus, glomerular and interstitial fibrosis could be related to epigenetic modifications through transcriptional

regulation.<sup>77,179–181</sup> The interest in epigenetics in clarifying hypertensive and diabetic CKD is increasing.

In this sense, as CKD incidence has been increasing in recent years, utilizing the potential therapeutic benefits of interventions to prevent esrD may be helpful in reducing the economic and clinical impact of CKD.<sup>18</sup>

## Conclusions

Interesting approaches to in-depth pharmacogenetics are increasing for tailored medicine. In fact, nowadays, high-risk CKD patients could be detected by genotype information. Nevertheless, these techniques assume high cost and must be optimized alongside classical clinical tests. Advances in technology in gene sequencing with epigenetic investigation, as well as well-designed studies on gene–gene interactions, gene–environment interactions, and DNA modifications (epigenetics), may improve our knowledge of CKD-related genes and subsequent patient care. These genetic markers could be useful for the prediction of CKD progression, but clinical risk factors remain more valuable in terms of prediction. However, further technical developments and epidemiological experimental data are still needed to demonstrate and establish the most cost-effective approach. The bulk of information in pharmacogenomics published nowadays is targeted at expanding this field of information, although physicians must be critical in their analysis and interpretation of the results.

Given that CKD is a complex disorder, and that it can benefit from genetic testing, further challenges include studying proteins, transcripts, and metabolites in order to correlate them with genetic data, improve clinical outcome, and lead to routine genetic tests in the clinical care of CKD.

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