Genomics in CKD: Is This the Path Forward?

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Recent advances in genomics and sequencing technology have led to a better understanding of genetic risk in CKD. Genetics could account in part for racial differences in treatment response for medications including antihypertensives and immunosuppressive medications due to its correlation with ancestry. However, there is still a substantial lag between generation of this knowledge and its adoption in routine clinical care. This review summarizes the recent advances in genomics and CKD, discusses potential reasons for its underutilization, and highlights potential avenues for application of genomic information to improve clinical care and outcomes in this particularly vulnerable population.
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INTRODUCTION

CKD affects an estimated 10% to 15% of individuals in the United States.[1] CKD is a largely asymptomatic yet serious condition associated with premature mortality, decreased quality of life, and increased health care expenditure. Untreated, it can result in ESRD and necessitate dialysis or kidney transplantation. It is also a major independent risk factor for cardiovascular disease (CVD), mortality and all-cause mortality.[2,3] Approximately two-thirds of CKD are attributable to diabetes (40% of CKD cases) and hypertension (28% of cases).[4] There exist significant racial and socioeconomic disparities in the incidence and progression of CKD.[5,6] African Americans/blacks disproportionately suffer from progressive CKD and more than 3-fold incidence of ESRD when compared to whites.[7,8]

There are currently no specific therapies for diabetes- and hypertension-associated CKD. The cornerstones of management include early diagnosis, accurate risk stratification, control of underlying illnesses such as diabetes and hypertension, and management of complications. The aims of this review were to summarize the recent advances in genomic understanding of CKD and highlight the potential future applications that genomic approaches might hold for the diagnosis, stratification, and management of this condition.

What Do We Know About Genomics and CKD?

CKD/ESRD clusters within families, and the heritability of estimated glomerular filtration rate has been estimated to be at 40% to 75% in population-based studies.[9,10] Using genome-wide association studies, multiple loci have been identified for CKD; however, the overall contribution to both estimated glomerular filtration rate and CKD disease understanding was minimal.[11-14]

However, one of the first major discoveries of genetic variants that significantly and substantially increases the risk of a chronic disease is a variant that increases the risk of CKD and ESRD by 5 to 10-fold. And, these high-risk variants are nearly exclusively found in people of African descent, thus contributing to the understanding of CKD disparities. This finding emerged from a search for genetic loci underlying disparities in focal segmental glomerulosclerosis that identified a genetic locus on the long arm of chromosome 22 and initially focused on the myosin, heavy chain 9, non-muscle gene (*MYH9*).[15,16] Further fine mapping and subsequent studies demonstrated that 2 distinct alleles of the *MYH9*-neighboring Apolipoprotein L1 (*APOL1*) gene confer substantially increased risk for a number of kidney diseases in African Americans, including focal segmental glomerulosclerosis, human immunodeficiency virus–associated nephropathy, and hypertension-attributable kidney disease.[17-19]

APOL1 risk alleles are defined by variants in the last exon of *APOL1*, which were found to confer resistance to lethal *Trypanosoma brucei* infections in sub-Saharan Africa, resulting in their selection and considerably higher frequency in individuals of African Ancestry compared with other populations.[20] This difference partly accounts for health disparities in kidney disease and ESRD in individuals of African descent.[17,21,22] This risk is particularly evident in adults with hypertension and without diabetes. There is also emerging evidence, that the APOL1 risk genotype may contribute to cardiovascular risk in African Americans.[23] In a recent study, APOL1 risk explained much of the cardiovascular burden disparity between Whites and African Americans.[24] After kidney transplant, shorter graft survival rates have been observed from donors with *APOL1* risk genotype.[25] This has influenced clinical practice, with some transplant centers testing and considering *APOL1* risk variants during the transplant evaluation for living donors.[26]

Does Genomics Risk Explain Racial Disparities in CKD?

Although the *APOL1* risk genotype increases the risk of CKD development and progression in people of African descent, particularly with hypertension, this does not

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explain all racial differences in CKD. First, having African ancestry and self-identifying in the social categories of African American or black are not completely linked. Second, a recent study in the Atherosclerosis Risk in Communities study demonstrated that high-risk *APOL1* variants did not associate with acute kidney injury (AKI) among African Americans, accounting for differences in income and/or insurance status attenuated the differences in AKI incidence between African Americans and Caucasians.[27] Considering that AKI and CKD are inextricably linked,[28] this highlights that other determinants of kidney disease disparities must be acknowledged. These include socioeconomic status, access to care, and social determinants of health.[29-33] Research will need to assess and address multiple (clinical, social, environmental, and genomic) reasons for CKD disparities.

Pharmacogenomics in CKD: An Avenue of Opportunity?

There are currently no specific, targeted therapies for the vast majority of patients with CKD. Current practice guidelines recommend tight control of blood pressure and/or hyperglycemia in particular in the presence of albuminuria to reduce ESRD and CVD risks in CKD patients.[34] One of the mainstays of therapy is blockade of the renin–angiotensin–aldosterone system (RAAS). This is a major pathway involved in the pathogenesis of diabetic nephropathy, and RAAS blockade with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) has been proven to reduce CKD progression.[35-37] The widespread use of RAAS blockers provides a potential avenue for pharmacogenomics study and intervention.

CLINICAL SUMMARY

- Recent advances in genomics and discovery of the apolipoprotein L1 risk genotype have explained a part of the racial disparities between blacks and whites, and genetic polymorphisms could explain the differences in treatment response with antihypertensives and immunosuppressive medications seen in blacks.
- Genetic differences are an important piece of the disparities-CKD puzzle; this information should not supplant already well-known sociodemographic reasons for disparities.
- Genomics could improve clinical outcomes and trial enrollment, but adoption by providers during routine clinical care is limited.
- Efforts are underway to educate patients and providers using a variety of resources and implement point of care and clinical decision support systems.

It is well known that there are significant racial/ethnic differences in response to antihypertensive. For example, African Americans/blacks respond more significantly to diuretics and calcium channel blockers than European Americans/whites, whereas their response to ACE inhibitors is less robust.[38] The ACE gene encodes ACE, a key enzyme involved in the RAAS. There is a high interindividual variability in circulating ACE levels, with a polymorphism located in intron 16 being the most extensively studied ACE genetic variant. The genetic diversity of ACE is particularly high in people of African descent. Although these differences could have sociodemographic components including access to care, the genomic part of this puzzle cannot be ignored. In the future, testing for this polymorphism may be useful for prediction of patient response to RAAS therapy. Studies also show that diabetic patients with differing genotypes of ACE gene have differing renal outcomes including mortality, decline in albuminuria, decreased blood pressure, and ESRD.[39-43] Thus, ACE genotype–guided therapy could provide a prototype for further investigation and implementation of pharmacogenomics-guided management in CKD.

Another important and actionable area related to pharmacogenomics and disparities is among kidney transplant recipients. With higher rates of ESRD than whites/European Americans, blacks/African Americans have poorer outcomes after transplant, including a 42% higher risk of graft loss at 5 years.[44] This disparity is, in part, due to inadequate immunosuppression, which can lead to allograft rejection. Among the mainstays of immunosuppression are calcineurin inhibitors, and one of the most commonly used is tacrolimus. Blacks require higher doses of tacrolimus than whites to have the same mean blood levels and thus the same immunosuppression.[45] This is in part because blacks are more commonly supermetabolizers of the drug. One reason for this difference is that common genetic variants in the cytochrome P450 system that control metabolism are more common in blacks (are virtually nonexistent in whites), and these variants lead to lower blood concentrations, even after adjusting for clinical factors.[45,46] Specifically, the wild-type gene, CYP3A5*1, which allows for significant production of CYP3A5, is reportedly absent in 60% to 90% whites and present in more than half blacks.[47] In fact, a recent clinical trial showed a lower dosing and favorable pharmacokinetic profile for blacks who were switched from twice-daily tacrolimus to an extended release formulation.[48] Again, there are other reasons for disparities in outcomes, including nonadherence to immunosuppressive agents, lack of adequate follow-up, social support and difficulty receiving medications.[49,50] However, genetic data can uncover patients who will need higher doses of tacrolimus as they are supermetabolizers, as opposed to being labeled as nonadherent due to their consistent low drug levels on monitoring.

Is Nephrology Keeping Pace With Genetic and Genomic Discoveries?

The few discoveries in genomics and nephrology to date are quite important and actionable. *APOL1* is one of the first genetic variants that have been shown to increase risk for a common chronic disease. Addressing disparities in metabolism of tacrolimus could greatly reduce racial disparities in survival after transplant.

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