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A Focus on APOL1 and Kidney Disease

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In the United States, the majority of cases of chronic kidney disease (CKD) and end-stage renal disease are attributed to diabetes mellitus and hypertension, disproportionately affecting individuals of African ancestry. The discovery of *apolipoprotein L-1* (*APOL1*) risk alleles has challenged our traditional views of "acquired" forms of CKD by highlighting the potential role of genetic factors in the development of kidney disease. *APOL1* risk genotypes, termed G1 and G2, are 2 common coding variants on chromosome 22 that significantly influence the risk of multiple forms of CKD among individuals of sub-Saharan African descent.[1] Following a recessive model, individuals with 2 risk alleles (either G1/G1, G2/G2, or G1/G2) are considered to have a high-risk genotype and up to a 10-fold higher risk for hypertension-attributed end-stage renal disease, a 10- to 17-fold higher risk of focal segmental glomerulosclerosis–associated end-stage renal disease, and increased rates of CKD progression and worsened allograft outcomes, than those with one or no risk variants.[1–4] The association of *APOL1* risk genotypes with nondiabetic nephropathies has put a spotlight on the role and ethical implications of routine *APOL1* testing in clinical care, particularly among potential kidney donors.[5,6] The role for *APOL1* screening is unclear, in part, because of a paucity of information on how to intervene on the basis of the *APOL1* status. Analyses from the African American Study of Kidney Disease and Hypertension (AASK) cohort and the Chronic Renal Insufficiency Cohort (CRIC) study demonstrated the absence of an interaction of either proteinuria or tight blood pressure control with a patient's *APOL1* status.[7] Without proven beneficial interventions, such as renin-angiotensin-aldosterone system blockade or tight blood pressure control that would mitigate the effects of *APOL1* risk genotypes on disease incidence or progression, the clinical utility (i.e., impact that knowledge of the variant would have on the clinical care) of knowing the *APOL1* status of a patient remains uncertain.

A necessary first step in understanding the role and clinical implications of routine *APOL1* screening is determining the prevalence of *APOL1* risk genotypes in the population of interest. Initially discovered in African Americans, *APOL1* risk genotypes have also been associated with increased CKD risk among self-identifying U.S. Hispanic/Latino populations, but with prevalence varying between Caribbean and non-Caribbean subpopulations because of differences in genetic admixture.[8]

In this issue of *Kidney International Reports*, investigators attempt to determine the prevalence of *APOL1* risk alleles in different subsets of the population in 2 countries (Democratic Republic of Congo and Brazil) on separate continents. In a pediatric cohort of 813 children, Ekulu *et al.*[9] found 6.4% had the high-risk genotype—lower than what has been found in other parts of sub-Saharan Africa and among African Americans in the United States. Although they reported an association between albuminuria and the high-risk genotype on unadjusted analysis, this association persisted in the subset of children with HIV on multivariable analyses. Among those without HIV, albuminuria was associated with elevated systolic blood pressure, but the authors did not assess whether there was an interaction between the elevated blood pressure, low estimated glomerular filtration rate, and the *APOL1* status. Of note, children with the high-risk genotype had a significantly higher blood pressure, and the proportion of patients with elevated pressure (defined as $>$ 95th percentile) was nearly double that seen in those without the high-risk genotype, underscoring the need for further study of the association. Riella *et al.*[10] reported on the *APOL1* status among a cohort of 274 Brazilian hemodialysis patients including 106

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patients who had first-degree relatives without CKD included in a case control study. They confirmed prior analyses that have demonstrated the occurrence of end-stage renal disease at an earlier age for individuals with *APOL1* risk genotypes. Not surprisingly, the high-risk genotype was nearly 10 times more frequent among dialysis patients than their first-degree relatives. Both studies highlight the need for assessment of variant frequencies among different subpopulations, particularly among populations with a potentially increased prevalence of these variants, who may be at increased risk for developing CKD. An accompanying commentary by Ross[11] discusses the insights that can be taken from these 2 studies.

In addition to understanding prevalence, more information is needed about factors that may contribute to disease susceptibility among individuals with the *APOL1* risk genotypes because not all individuals with these alleles will go on to develop CKD. *APOL1*-mediated kidney disease only occurs in a minority of individuals with the high-risk genotype, underscoring the need to identify modifiers that influence the development of CKD. Identification of factors that appear to be associated, such as HIV infection, which results in a 29-fold higher risk for nephropathy, supports the notion that *APOL1*-mediated kidney disease follows a two-hit model of disease development. Like the immunologic response of HIV infection, secondary factors may be environmental or genetic. Thus, there is pressing need for additional studies to identify potential triggers that will enable us to better identify individuals most at risk for developing CKD from those who are not. Two studies included in this issue attempt to expand on our understanding of factors that may act as a "second hit." Nqebelele *et al.*[12] examined the role of JC virus infection among black South Africans with CKD and *APOL1* risk genotypes, and the authors appear to confirm the previously reported protective effects of JC viruria on allograft outcomes.[13] Pike *et al.*[14] examined the role of metabolic acidosis and dietary acid load as a potential modifying factor among African American participants in the CRIC study. Although their study seems to be inadequately powered, there appears to be little evidence of a large impact of a high acid load as a second hit among individuals with the *APOL1* risk genotypes. These studies add incremental gains to our understanding of *APOL1*-associated nephropathy, as we try to understand the role of *APOL1* in CKD occurrence and progression. A commentary by Husain and Chang further discusses the relevance of environmental factors in developing kidney disease in individuals with *APOL1* risk genotypes.[15]

Although there is no current evidence that knowledge of *APOL1* status will inform clinical practice or impact patient outcomes, we are in the early stages of understanding the role of *APOL1* in CKD. Much remains to be learned about the pathogenesis of kidney injury in individuals with the high-risk genotype including identification of both second hits and protective factors. As a result, it remains premature to suggest routine *APOL1* screening at present, especially given that it may unintentionally expose vulnerable and underrepresented communities to unintended harm such as discrimination, further marginalization, or worsening of health-related disparities, such as through increased barriers to living organ donation. Additional studies that shed light on the prevalence as well as other modifiers of risk for individuals with this genetic variant are urgently needed. Only then will we understand how to use this genetic marker of disease risk to improve the care of individual patients.

DISCLOSURE

All the authors declared no competing interests.

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