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Searching for Second Hits for the Development of *APOL1*-Associated Kidney Disease

S. Ali Husain[1] and Jae-Hyung Chang[1]

[1]Department of Medicine, Division of Nephrology, Vagelos College of Physicians and Surgeons, Columbia University Medical Center, New York, New York, USA

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The near decade since the identification of *APOL1* risk alleles as risk factors for the development of kidney disease has yielded dramatic improvements in our understanding of the increased risk of kidney disease in individuals of African ancestry. However, major gaps in our knowledge remain, particularly in delineating the role of "second hits" that lead to the development of clinically relevant kidney disease in individuals with risk genotypes (G1/G1, G2/G2, or G1/G2). Although up to 32% of individuals in select populations have risk genotypes, only a minority will develop clinical chronic kidney disease (CKD) and end-stage kidney disease.[1] A recent genome-wide association study suggested that environmental factors, rather than gene-gene interactions, are predominantly responsible for this observation.[2] The ongoing effort to identify these environmental factors is therefore crucial to any attempt to mitigate the risk of the development or progression of *APOL1*-associated kidney disease. In this issue of *Kidney International Reports*, 2 studies attempt to shed light on potential factors that may serve as second hits leading to the development of kidney disease in individuals with *APOL1* risk genotypes.

Nqebelele and colleagues[3] examined JC viruria as a potential protective factor against the development of CKD by comparing the prevalence of JC viruria in patients with hypertensive nephropathy compared with healthy first-degree relatives and unrelated controls. Viral infections have largely been described as triggers for, rather than protective against, the development of collapsing glomerulopathy in individuals with high-risk *APOL1* genotypes, including HIV, parvovirus B19, cytomegalovirus, or the BK polyomavirus. These associations are thought to result, among others, from proinflammatory cytokine expression, most notably interferon-mediated APOL1 expression. In contrast, JC viruria has been demonstrated in multiple studies to be associated with a decreased risk of kidney disease (either reduced estimated glomerular filtration rate [eGFR] or albuminuria) independent of *APOL1* genotype, potentially causatively through protection against other viruses via anti-polyomavirus antibodies or protective changes in cellular function.[4,5]

In the current study, the authors again demonstrated a lower prevalence of JC viruria in 64 black patients of South African ancestry with hypertension-attributed CKD (3%) compared with 44 first-degree relatives (24%) and 56 unrelated controls (36%).[3] This degree of difference is striking, considering that we may reasonably predict a similar prevalence of viruria in patients and first-degree relatives based on shared exposure risk factors. The proportion of participants in each group with *APOL1* risk genotypes was similar (11% vs. 5% vs. 9%, respectively). After adjusting for demographic factors and *APOL1* genotype, there remained a 16-fold increased odds of CKD in individuals without viruria. Notably, no participants in the case group had BK viruria, and its prevalence was low in the other groups as well (11% for relatives and 4% for unrelated controls). Overall, these consistent results in a new population further support the notion that the absence of JC virus may indeed represent a harbinger for the development of CKD and end-stage renal disease, and that prior findings were not simply the result of chance or local factors.

Nevertheless, it remains to be seen whether the observed association is due to a direct effect of the JC virus, such as through competitive inhibition of other

Correspondence: S. Ali Husain, Division of Nephrology, Vagelos College of Physicians and Surgeons, Columbia University Medical Center, 622 West 168th Street, PH4–124, New York, New York 10032, USA. E-mail: SAH2134@cumc.columbia.edu

viral replication, or simply reflects underlying differences between individuals with or without viruria after viral exposure, perhaps reflecting higher levels of host factors, such as interferon, that contribute to both viral eradication and CKD development.[5] Further, the impact of JC viruria on the development of kidney disease specifically in individuals with high-risk *APOL1* genotypes cannot be elucidated with these data given the small number of study participants with 2 risk alleles that precludes a subanalysis of just this group. In light of the limitations of the cross-sectional data available, a large, prospective cohort study examining the risk of CKD and end-stage kidney disease over time is warranted to better understand the findings of these studies and to examine a potential interaction between viruria and *APOL1* genotype.

Pike *et al.*[6] performed such a prospective analysis to examine the interaction between dietary acid load and *APOL1* genotype on the progression of CKD among a large cohort of 1048 black Americans in the Chronic Renal Insufficiency Cohort study, 20% of whom had an *APOL1* risk genotype. The relationship between metabolic acidosis and faster progression of CKD has previously been demonstrated in other cohort studies (including a prior analysis of data from the Chronic Renal Insufficiency Cohort), with additional small studies showing alkali supplementation to be effective in reducing glomerular filtration rate loss over time.[7,8] This association has been attributed to activation of hormonal and inflammatory pathways that promote interstitial fibrosis in patients with acidosis and CKD.[7] Given prior evidence that *APOL1* risk genotypes are also associated with faster loss of eGFR over time, potential interactions between genotype and the modifiable risk factors of acidosis and dietary acid load were plausible.

However, although Pike *et al.*[6] found that acidosis, defined as serum CO_2 concentration <22 mEq/l, was associated with an elevated rate of halving of eGFR in bivariable analyses, this relationship was attenuated after adjusting for baseline eGFR, albuminuria, and patient comorbidities and demographics. An association between patient-reported dietary acid load and eGFR loss also was absent. Further, findings were similar between patients with and without *APOL1* risk genotypes. These results seem to contradict the prior data from the Chronic Renal Insufficiency Cohort, as well as from the African American Study of Kidney Disease and Hypertension.[8,9] In the latter analysis, lower serum bicarbonate level was significantly associated with increased risk of end-stage kidney disease or eGFR reduction by 50% or 25 ml/min per 1.73 m^2 in a cohort of African American individuals with CKD.[9] The difference in results compared with the current study may partially reflect unequal cohort characteristics (differences in age, proteinuria, and prevalence of baseline congestive heart failure and cardiovascular disease), number and choice of covariates for adjusted models (income, education, and degree of African ancestry genotype were not considered in the African American Study of Kidney Disease and Hypertension), and thresholds for group definitions. Importantly, the African American Study of Kidney Disease and Hypertension analysis also found that accounting for calculate protein intake had no impact on the observed relationship between acidosis and the composite renal endpoint. Given this combination of results in the 2 studies, the relationship between acidosis and CKD progression in individuals with *APOL1* risk genotypes therefore requires further examination in a larger cohort, as does the use of alkali supplementation to reduce glomerular filtration rate loss over time in this population. For now, given the body of prior literature pertaining to the other deleterious effects of acidosis, continued use of alkali therapy appears to be the most reasonable approach.

Ultimately, these studies highlight the gaps in knowledge that remain in our understanding of why certain individuals with *APOL1* risk genotypes develop CKD/end-stage kidney disease, whereas many others do not. Further studies to better understand the pathomechanisms of *APOL1*-associated kidney disease, including identification of potential second hits, are desperately needed.

DISCLOSURE

All the authors declared no competing interests.

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