Examination of Potential Modifiers of the Association of APOL1 Alleles with CKD Progression

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Abstract

Background and objectives Common apolipoprotein L1 (APOL1) variants are associated with increased risk of progressive CKD; however, not all individuals with high-risk APOL1 variants experience CKD progression. Identification of factors contributing to heterogeneity has important scientific and clinical implications.

Design, setting, participants, & measurements Using multivariable Cox models, we analyzed data from 693 participants in the African American Study of Kidney Disease and Hypertension to identify factors that modify the association between APOL1 genotypes and CKD progression (doubling of serum creatinine or incident ESRD).

Results Participant mean age was 54 years old, median GFR was 49 ml/min per 1.73 m², and 23% had the APOL1 high-risk genotype (two copies of the high-risk allele). Over a mean follow-up of 7.8 years, 288 (42%) participants experienced CKD progression. As previously reported, the high-risk genotype was associated with higher risk of CKD progression compared with the low-risk genotype (hazard ratio [HR], 1.88; 95% confidence interval [95% CI], 1.46 to 2.41). Although we found some suggestion that obesity (HR, 1.48; 95% CI, 1.05 to 2.08 and HR, 2.44; 95% CI, 1.66 to 3.57 for body mass index ≥30 versus <30 kg/m²; P interaction =0.04) and increased urinary excretion of urea nitrogen (HR, 1.43; 95% CI, 0.98 to 2.09 versus HR, 2.33; 95% CI, 1.65 to 3.30 for urine urea nitrogen ≥8 versus <8 g/d; P interaction =0.04) were associated with lower APOL1–associated risk for CKD progression, these findings were not robust in sensitivity analyses with alternative cut points. No other sociodemographic (e.g., education and income), clinical (e.g., systolic BP and smoking), or laboratory (e.g., net endogenous acid production, urinary sodium and potassium excretions, 25-hydroxy vitamin D, intact parathyroid hormone, or fibroblast growth factor 23) variables modified the association between APOL1 and CKD progression (P interaction >0.05 for each).

Conclusions Sociodemographic factors and common risk factors for CKD progression do not seem to alter APOL1–related CKD progression. Additional investigation is needed to identify nontraditional factors that may affect the association between APOL1 and progressive CKD.


Introduction

In recent years, genetic variants encoding apolipoprotein L1 (APOL1) have emerged as a risk factor for ESRD among African Americans (1–4). The presence of two APOL1 risk variants (G1 and G2) on chromosome 22 confers protection against the parasite Trypanosoma brucei rhodesiense; the same genetic variants have also been associated with increased risk for various forms of kidney disease. These include hypertension–attributed CKD, FSGS, and HIV-associated nephropathy (HIVAN) among others (2,3,5,6).

In the African American Study of Kidney Disease and Hypertension (AASK) and the Chronic Renal Insufficiency Cohort, Parsa et al. (1) showed that individuals with two APOL1 risk alleles (high-risk genotype) were more likely to experience CKD progression than those with one or no copies (low-risk genotypes). These findings suggest that APOL1 risk variants partially account for the excess burden of ESRD observed in African Americans (1,4,7); however, not all individuals with the APOL1 high-risk genotype develop ESRD or even CKD (1,4).

Additional genetic and/or nongenetic factors seem to modify the risk of kidney disease progression in individuals with the high-risk APOL1 genotype (8). One such example is HIVAN. Although individuals with two APOL1 high–risk alleles have a 4.25% lifetime risk of developing FSGS, those additionally infected with HIV have a 50% lifetime risk of developing HIVAN (6). Moreover, control of HIV infection with highly active antiretroviral therapy reduces the risk of CKD in patients with the APOL1 high–risk genotype (8–10). In another example, Divers et al. (11) reported that the presence of JC virus may be protective against kidney disease among individuals with two APOL1 high–risk alleles. Divers et al. (11) hypothesized that infection with the JC virus may inhibit infection by other viruses that are nephropathic or alter the transcription of genes involved in pathways of apoptosis and autophagy.
More recently, Tin et al. (12) found that higher levels of hemostatic factors (factor VIIIc and protein C) were associated with an increased risk for ESRD and that this association was more pronounced in African Americans with two APOL1 high-risk alleles. Finally, Divers et al. (13) have also described interactions between single-nucleotide polymorphisms in the podocin (NPHS2), serologically defined colon cancer antigen 8 (SDCCAG8), and (near) bone morphogenetic protein 4 (BMP4) genes and APOL1-associated ESRD. Thus, although APOL1 high-risk variants are associated with an increased risk for CKD, this risk may be augmented or reduced by certain genetic, environmental, or clinical factors yet to be fully elucidated (8).

We sought to examine potential modifying risk factors in the association between APOL1 high-risk genotype status and CKD progression among African Americans with hypertension-attributed nephropathy in AASK to inform future studies and interventions targeting individuals at greatest risk for APOL1-associated nephropathy.

Materials and Methods
Study Population and Design
The AASK study initially began as a trial (1,14–16). From 1995 to 2001, 1094 African Americans with CKD attributed to hypertension were randomized to a mean arterial BP goal of ≤130/80 mmHg (standard control group). Each participant was also randomly assigned to initial therapy with one of three BP medications: ramipril, metoprolol, or amlodipine (14). At the end of the trial phase, those individuals who had not yet developed ESRD were invited to enroll in the cohort phase, which began in April of 2002 and continued through 2007. During this time, all cohort participants were transitioned to ramipril therapy with a goal BP of <140/90 mmHg until 2004, when this goal was further lowered to <130/80 mmHg because of changes in national guidelines. Institutional review boards at each study center approved protocols for both the trial and cohort phases, and all study participants provided written informed consent (16). We used data from both the trial and cohort phases of AASK.

Of 836 AASK Trial participants who also consented to DNA testing, 693 were successfully genotyped for APOL1 risk variants and included in our study (1). These individuals were similar to participants who had provided genetic consent but had unsatisfactory genotyping. Compared with those who did not provide DNA or consent for genetic testing, our study population was younger and had higher body mass index (BMI), higher mean baseline 125 iohamateal GFR (iGFR), and less proteinuria (1).

Outcomes and Predictors
The primary outcome was time from baseline to CKD progression defined as a doubling of serum creatinine from baseline or the development of ESRD (dialysis or renal transplantation) (16). Serum creatinine was measured at baseline and subsequent 6-month intervals (14,16).

We examined several sociodemographic and clinical risk factors as potential effect modifiers of the association between APOL1 risk status and CKD progression. Participants had previously been genotyped for the APOL1 G1 (rs73885319 or rs60910145) and G2 (rs71785313) risk alleles using ABI Taqman (Applied Biosystems, Foster City, CA); 140 ancestry informative markers were also genotyped, and percentage of European ancestry was determined using ANCESTRYMAP (17). On the basis of a recessive genetic model, high-risk status was defined as having two copies of these APOL1 risk alleles, whereas low-risk status was defined as having one or no copies. Additional details on APOL1 genotyping in AASK have previously been described (1).

Candidate modifiers were selected on the basis of their prior association with CKD, potential modifiability, and/or theoretical relationship with inflammation. These included age, sex, education, income, smoking status, systolic BP, BMI, baseline iGFR, total cholesterol, HDL, hematocrit, serum uric acid, serum phosphorus, calcium-phosphate product, and net endogenous acid production (NEAP) as well as dietary sodium, potassium, and protein intake as measured by 24-hour urine sodium, potassium, and urea nitrogen, respectively (18,19). NEAP was estimated using the following equation: NEAP (milliequivalents per day) = 10.2+54.5 (protein intake [grams per day]/potassium intake [milliequivalents per day]), which has previously been validated (20,21). Mineral metabolite data (fibroblast growth factor 23 [FGF-23], intact parathyroid hormone [iPTH], and 25-hydroxy vitamin D) at 12 months of follow-up were also studied (22).

Statistical Analyses
Baseline characteristics were compared by APOL1 risk status using t tests and Wilcoxon rank sum tests for continuous variables and Fisher’s exact tests for categorical variables. A series of Cox proportional hazards models was then constructed to assess the association between APOL1 risk status and CKD progression. Consistent with the study by Parsa et al. (1), our base model adjusted for age, sex, percentage of European ancestry, and baseline iGFR. Stratified analyses by dichotomized clinical factors were then conducted to assess for effect modification. For continuous variables, strata cut points were determined using the median or values considered to be of clinical significance. We also performed analyses using the total sample, with an interaction term between each potential modifier and APOL1 risk status.

To assess the robustness of our findings, sensitivity analyses were conducted as follows: (1) using the 75th percentile as an alternative cut point and (2) treating the factor of interest as a continuous variable. For variables that seemed to modify the APOL1-associated risk for CKD progression (e.g., BMI and urinary excretion of urea nitrogen [UUN]), additional analyses introducing spline terms with alternative knot points were also performed. Participants were censored when they were lost to follow-up or died. Otherwise, they underwent administrative censoring on June 30, 2007 when outcome ascertainment for AASK ended (16). The proportional hazards assumption was confirmed graphically and by Schoenfeld residuals.

A similar series of Cox proportional hazards models was constructed for analyses involving 25-hydroxy vitamin D, iPTH, and FGF-23. However, given that data for these variables were only available at 12 months, the time of entry for these analyses was shifted to 12 months. We also
adjusted for age, sex, percentage of European ancestry, and iGFR (splined with knot at 60 ml/min per 1.73 m²) at 12 months. A spline was introduced for iGFR at 12 months, because model checking revealed nonlinearity in the association between iGFR and the log hazard of CKD progression. Each mineral metabolite was treated as follows: (1) stratified at the median, (2) stratified at the 75th percentile, (3) as a continuous variable, and (4) as a natural log-transformed continuous variable. The proportional hazards assumption was confirmed graphically.

Data were analyzed using Stata statistical software (version 12, 2011; College Station, TX). P values <0.05 were considered to be statistically significant.

Results

Baseline Characteristics

The baseline characteristics of 693 AASK participants included in our study are presented in Table 1. Among them, 160 individuals (23% of participants) carried the APOL1 high-risk genotype, whereas 533 individuals had the low-risk genotype. The APOL1 high-risk group was younger with lower baseline iGFR; lower systolic, diastolic, and mean arterial BPs; higher serum uric acid; and more proteinuria compared with the APOL1 low-risk group (P<0.05 for each comparison). At 12 months, median FGF-23 was also significantly higher in the APOL1 high-risk group (P=0.02), potentially reflecting the lower baseline iGFR observed in this group. There was no statistically significant difference in median iPTH or 25-hydroxy vitamin D levels (P=0.30 and 0.06, respectively).

Association between APOL1 and CKD Progression

During a mean follow-up of 7.8 years, 288 (42%) individuals experienced CKD progression defined as doubling of serum creatinine or incident ESRD. This included 93 (58%) individuals from the APOL1 high-risk group and 195 (37%) individuals from the APOL1 low-risk group. Using a recessive genetic model, we confirmed that individuals with the high-risk genotype had a 1.88-fold higher hazard risk of CKD progression (95% confidence interval [95% CI], 1.46 to 2.41; P=0.001) than among nonobese (BMI<30 kg/m²; n=349) individuals (adjusted hazard ratio [HR], 1.48; 95% CI, 1.05 to 2.08) than among nonobese (BMI<30 kg/m²; n=344) individuals (adjusted HR, 2.44; 95% CI, 1.66 to 3.57; P interaction =0.04). However, when additional analyses were conducted stratifying the data at the 75th percentile or treating BMI as a continuous variable, these associations did not persist (P interaction =0.92 and 0.67, respectively). Additional analyses including splines with knot points at BMI of 20, 25, 30, 35, or 40 kg/m² also failed to show a differential effect of BMI on the association between APOL1 and CKD progression (P interaction >0.05 for all). At baseline, individuals with obesity were more likely to be younger or women, while having less education, greater proteinuria, higher mean arterial and diastolic BPs, higher serum glucose, lower albumin, and worse lipid profiles compared with their leaner counterparts (Supplemental Table 1).

UUN≥8 g/d was also associated with a lower APOL1-associated risk for CKD progression (adjusted HR, 1.43; 95% CI, 0.98 to 2.09 for UUN≥8 g/d [n=326] versus adjusted HR, 2.33; 95% CI, 1.65 to 3.30 for UUN<8 g/d [n=366]; P interaction =0.04) (Figure 2). However, when reanalyzed using the 75th percentile as a cut point or treating UUN as a continuous variable, these findings were no longer statistically significant (P interaction =0.43 and 0.14, respectively). Similarly, analyses including splines with knot points at UUN of 4, 6, 8, 10, or 12 g/d did not show a differential effect of UUN on the association between APOL1 and CKD progression (P interaction >0.05 for all). At baseline, those with increased UUN excretion were more likely to be men and had higher iGFR, higher serum glucose, lower HDL, and less proteinuria (Supplemental Table 1). Of note, both obesity and elevated UUN were directly associated with an increased risk for CKD progression (Supplemental Table 2).

None of the other sociodemographic, clinical, and laboratory variables (age, sex, education, income, smoking status, systolic BP, baseline iGFR, total cholesterol, HDL, hematocrit, uric acid, calcium-phosphate product, serum phosphorus, urine sodium and potassium, and NEAP) examined significantly modified the association between APOL1 high-risk status and CKD progression (P>0.05 for each comparison). In sensitivity analyses, similar conclusions were obtained when treating each candidate modifier as a continuous variable or using an alternative cut point at the 75th percentile (P>0.05 for each comparison). Mineral metabolic data (25-hydroxy vitamin D, iPTH, and FGF-23) were only available at 12 months of follow-up; analyses involving these variables were, therefore, conducted with time entry shifted to 12 months. We found that none of these three additional variables modified the association between APOL1 and CKD progression (P>0.05 for each comparison; data not shown).

Discussion

The aim of this study was to identify patient characteristics that modify the association between APOL1 genotype status and kidney disease progression among African Americans with hypertension-attributed nephropathy. We examined 21 clinical and laboratory factors and report that, although there seemed to be a lower effect of APOL1 high-risk genotype status on CKD progression among individuals with obesity or greater UUN, these findings did not persist in sensitivity analyses. None of the other variables examined had a significant effect on the association between APOL1 high-risk genotype status and CKD progression.

Multiple studies have now shown that having two APOL1 high-risk variants is associated with an increased risk for both the development of CKD and its progression to ESRD (1,4,5). Parsa et al. (1) reported that, among AASK participants, those with two APOL1 high-risk alleles had an 88% higher hazard of experiencing CKD progression compared with those with one or no risk alleles (P<0.001). Parsa et al. (1) also assessed for potential interactions between APOL1
and baseline proteinuria, randomized BP medication, or randomized BP goal, but each of the corresponding interaction tests was nonsignificant (P interaction =0.16, 0.72, and 0.72, respectively). Importantly, 40% of individuals with two APOL1 high-risk alleles did not reach the primary outcome of ESRD or doubling of serum creatinine (1). Thus, determining why some individuals with this high-risk genetic background experience adverse kidney outcomes, whereas others do not is critically important.

Our study examined numerous sociodemographic, clinical, and laboratory variables that are relevant to patients with kidney disease. We found that the majority of these factors did not modify the association between APOL1 high-risk variants and progressive CKD. One potential explanation for these negative findings is that most participants in AASK had established CKD at the time of enrollment (1,16). Perhaps, some of the factors that we examined do still affect APOL1 risk allele status.

### Table 1. Baseline characteristics of study participants by APOL1 risk allele status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Low-Risk APOL1: Zero or One Risk Alleles</th>
<th>High-Risk APOL1: Two Risk Alleles</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>693</td>
<td>533</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Age at randomization, yr</td>
<td>54.9 (46.6–62.8)</td>
<td>55.7 (48.4–63.2)</td>
<td>52.8 (43.5–62.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Women</td>
<td>279 (40%)</td>
<td>210 (39%)</td>
<td>69 (43%)</td>
<td>0.41</td>
</tr>
<tr>
<td>European ancestry, %</td>
<td>0.13 (0.07–0.22)</td>
<td>0.14 (0.07–0.22)</td>
<td>0.13 (0.07–0.20)</td>
<td>0.47</td>
</tr>
<tr>
<td>Family history of ESRD</td>
<td>94 (14%)</td>
<td>73 (14%)</td>
<td>21 (13%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Smoker</td>
<td>Current</td>
<td>195 (28%)</td>
<td>150 (28%)</td>
<td>45 (28%)</td>
</tr>
<tr>
<td>Past</td>
<td>202 (29%)</td>
<td>159 (30%)</td>
<td>43 (27%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>296 (43%)</td>
<td>224 (42%)</td>
<td>72 (45%)</td>
<td></td>
</tr>
<tr>
<td>Annual income</td>
<td>Low ($0–$14,999)</td>
<td>323 (47%)</td>
<td>250 (47%)</td>
<td>73 (46%)</td>
</tr>
<tr>
<td>Mid/high ($15,000)</td>
<td>234 (34%)</td>
<td>182 (34%)</td>
<td>52 (33%)</td>
<td></td>
</tr>
<tr>
<td>Declined to answer</td>
<td>136 (20%)</td>
<td>101 (19%)</td>
<td>35 (22%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>High school degree</td>
<td>412 (60%)</td>
<td>316 (59%)</td>
<td>96 (60%)</td>
</tr>
<tr>
<td>No high school degree</td>
<td>280 (40%)</td>
<td>216 (41%)</td>
<td>64 (40%)</td>
<td></td>
</tr>
<tr>
<td>Randomized BP goal group</td>
<td>Low</td>
<td>351 (51%)</td>
<td>270 (51%)</td>
<td>81 (51%)</td>
</tr>
<tr>
<td>Standard</td>
<td>342 (49%)</td>
<td>263 (49%)</td>
<td>79 (49%)</td>
<td></td>
</tr>
<tr>
<td>Randomized drug group</td>
<td>Ramipril</td>
<td>290 (42%)</td>
<td>224 (42%)</td>
<td>66 (41%)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>271 (39%)</td>
<td>205 (38%)</td>
<td>66 (41%)</td>
<td></td>
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<tr>
<td>Amlodipine</td>
<td>132 (19%)</td>
<td>104 (20%)</td>
<td>28 (18%)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>150±24</td>
<td>152±25</td>
<td>146±22</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>96±15</td>
<td>97±15</td>
<td>94±14</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>114±16</td>
<td>115±17</td>
<td>111±15</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.1±6.7</td>
<td>30.9±6.5</td>
<td>31.7±7.2</td>
<td>0.23</td>
</tr>
<tr>
<td>iGFR, ml/min per 1.73 m²</td>
<td>49 (37–59)</td>
<td>51 (38–59)</td>
<td>44 (32–55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>211±44</td>
<td>211±44</td>
<td>213±44</td>
<td>0.68</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>48±15</td>
<td>48±16</td>
<td>49±15</td>
<td>0.40</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>39.5±5</td>
<td>39.4±4.8</td>
<td>39.9±5.4</td>
<td>0.35</td>
</tr>
<tr>
<td>Serum uric acid, mg/dl</td>
<td>8.3±1.8</td>
<td>8.2±1.9</td>
<td>8.5±1.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum phosphorus, mg/dl</td>
<td>3.5±0.5</td>
<td>3.5±0.5</td>
<td>3.5±0.5</td>
<td>0.91</td>
</tr>
<tr>
<td>Serum ca-phos product, mg²/dl²</td>
<td>31.8±4.8</td>
<td>31.7±4.8</td>
<td>31.9±4.8</td>
<td>0.74</td>
</tr>
<tr>
<td>Urine sodium, g/d</td>
<td>3.5 (2.3–4.8)</td>
<td>3.5 (2.3–4.7)</td>
<td>3.3 (2.3–4.9)</td>
<td>0.97</td>
</tr>
<tr>
<td>Urine potassium, g/d</td>
<td>1.6 (1.2–2.2)</td>
<td>1.6 (1.2–2.2)</td>
<td>1.6 (1.1–2.3)</td>
<td>0.51</td>
</tr>
<tr>
<td>Urine urea nitrogen, g/d</td>
<td>7.8 (5.9–10.2)</td>
<td>7.8 (5.9–10.2)</td>
<td>7.8 (6.0–10.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>Urine protein, g/g Cr</td>
<td>0.1 (0.03–0.3)</td>
<td>0.1 (0.03–0.2)</td>
<td>0.2 (0.04–0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NEAP, meq/d</td>
<td>70.5 (53.1–92.9)</td>
<td>70.4 (53.3–90.5)</td>
<td>70.9 (51.8–97.1)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**At 12 mo of follow-up**

<table>
<thead>
<tr>
<th>Value</th>
<th>All</th>
<th>Low-Risk APOL1: Zero or One Risk Alleles</th>
<th>High-Risk APOL1: Two Risk Alleles</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>565</td>
<td>439</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>FGF-23, pg/ml</td>
<td>44.6 (30.5–64.1)</td>
<td>42.1 (29.2–62.4)</td>
<td>48.8 (36.4–67.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>iPTH, pg/ml</td>
<td>35.7 (23.4–60.5)</td>
<td>34.7 (22.9–60.4)</td>
<td>38.6 (25.1–61.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>25-hydroxy vitamin D, ng/ml</td>
<td>13.6 (9.1–19.3)</td>
<td>14.2 (9.3–19.4)</td>
<td>11.0 (8.3–18.7)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Values are presented as means ± SDs, medians (interquartile ranges), or n (%). APOL1, apolipoprotein L1; iGFR, i¹²⁵Iothalamate GFR; ca-phos, calcium-phosphate; Cr, creatinine; NEAP, net endogenous acid production; FGF-23, fibroblast growth factor 23; iPTH, intact parathyroid hormone.
but their effect occurs earlier in the course of CKD. Alternatively, other factors that we did not examine might modify the risk of CKD progression associated with APOL1 high–risk variants. Interactions with other factors, particularly those that are modifiable, should be explored in future studies.

Of all of the factors examined, only higher BMI (≥30 kg/m²) and UUN (≥8 g/d) seemed to be associated with a lower APOL1-associated risk of CKD progression. Obesity and protein-rich diets (as reflected...
by a higher UUN) have been hypothesized to lead to glomerular hyperfiltration and subsequent glomerular sclerosis (23–27). The most plausible explanation as to why higher BMI and UUN were associated with a decreased APOL1 risk for adaptive forms of CKD progression is that these other non-APOL1–mediated pathways were occurring. Alternatively, an incremental deleterious effect of APOL1 risk variants on CKD progression may not have been observed among individuals with obesity or high UUN, because downstream pathways (e.g., apoptosis and autophagy) involving APOL1 may already be dysregulated in these individuals (28–31). Finally, it is possible that our findings related to BMI and UUN may have been due to chance or residual confounding, because their significance did not persist in sensitivity analyses. Therefore, our results should be interpreted with caution.

APOL1 belongs to a family of APO genes encoding for lipoproteins with functions that are largely unknown, although they seem to have a role in innate immunity against intracellular pathogens and are involved in lipid transport. Unlike other members of the APOL family, APOL1 possesses a signal peptide that allows for APOL1 to be exported out of the cell and into the bloodstream, where it associates with HDL particles. APOL1 is also believed to play a role in programmed cell death and autophagy (32,33). Recently, Nichols et al. (34) showed that the expression of APOL1 in podocytes and endothelial cells is induced by IFNs and Toll–like receptor agonists, suggesting a role for inflammation as a CKD inducer. Perhaps, the individuals with obesity or elevated UUN in our study were less likely to be malnourished and hence, had less inflammation to drive APOL1 expression (35). However, other studies have shown that obesity is associated with a low–grade chronic inflammation in response to metabolic surplus by adipocytes and other specialized metabolic cells (36).

Although we did not find that HDL modified the association between APOL1 and CKD progression, a prior study has shown that higher HDL is paradoxically associated with lower eGFR among African Americans, particularly those with two copies of the G1 variant rs73885319 (p.S342G) (37). In our study, both individuals with obesity and increased UUN were noted to have lower mean HDL levels at baseline. Perhaps, the antioxidant or anti-inflammatory properties of HDL differ among individuals with APOL1 high-risk variants, and having lower levels of this altered HDL provides protection against CKD progression (37). Additional studies are needed to better elucidate whether the APOL1 risk alleles lead to kidney disease through abnormalities in lipid metabolism.

Our study has limitations. First, we used only baseline variables and did not account for changes in covariates over time. Second, our results may not be generalizable to other CKD populations, because the AASK study was limited to African Americans with CKD attributed to hypertension. Third, although AASK is one of the larger cohort studies with APOL1 data, our sample size may have limited our ability to detect statistically significant gene-environment interactions. Fourth, we used total rather than bioavailable 25-hydroxy vitamin D, the latter of which was not measured in AASK. Still, the optimal approach to measuring bioavailable 25-hydroxy vitamin D remains under debate (38–41). Strengths of our study include a well characterized cohort of African Americans with CKD, long duration of follow-up, and data that were collected prospectively. Furthermore, our study is one of the first to examine a comprehensive array of potential noninfectious modifiers of the association between APOL1 high–risk variants and CKD progression.

In conclusion, we found that obesity and increased UUN were associated with a lower APOL1–associated risk for progressive CKD among African Americans with hypertension–attributed CKD, but these findings were not robust. Additional investigation is warranted to determine whether other factors (e.g., environmental or genetic) affect the association of APOL1 risk variants with CKD progression, because the identification of such factors could have important therapeutic implications.

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Disclosures

T.K.C. formerly owned stock in Pfizer Pharmaceuticals. The other authors have nothing to declare.

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