Patterns of Kidney Function Decline Associated with APOL1 Genotypes: Results from AASK

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Abstract

Background and objectives Trajectories of eGFR in patients with CKD are highly variable. Only a subset of patients with CKD experiences a steady decline in eGFR. The objective of our study was to investigate whether eGFR trajectory patterns differ by *APOL1* risk status.

Design, setting, participants, & measurements Our study was a longitudinal observational study of 622 participants in the African American Study of Kidney Disease and Hypertension with *APOL1* genotyping and sufficient follow-up for estimating GFR trajectories. The predictor was *APOL1* high–risk status (having two copies of the G1 or G2 risk alleles) versus low-risk status (zero or one copy of the risk alleles), and the outcome was four eGFR trajectory patterns on the basis of the joint probabilities of linearity and progression: steady decline, unsteady decline, steady stable, and unsteady stable.

Results Over a median follow-up of 9 years, 24.0% of participants experienced steady eGFR decline, 25.9% had an unsteady decline, 25.6% were steady and stable, and 24.6% were unsteady but stable. Those experiencing steady decline had lower eGFR and higher urine protein-to-creatinine ratio at baseline than participants with the other eGFR trajectory patterns. The *APOL1* high–risk group was associated with a greater odds for the steady decline pattern than the *APOL1* low–risk group (unadjusted odds ratio, 2.45; 95% confidence interval, 1.62 to 3.69). This association remained significant after adjusting for demographic factors, baseline eGFR, urine protein-to-creatinine ratio, treatment assignment, and follow-up time (adjusted odds ratio, 1.59; 95% confidence interval, 1.00 to 2.52).

Conclusions Among patients with CKD attributed to hypertension, those with the *APOL1* high–risk genotype were more likely to experience a steady decline trajectory in eGFR than those without the *APOL1* high–risk genotype. These findings suggest a persistent underlying pathophysiologic process in those patients with the *APOL1* high–risk genotype.

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Introduction

The decline of kidney function in the general population and the progression of CKD to ESRD are highly variable (1–4). Some individuals may experience an unremitting decline in eGFR, whereas others maintain stable eGFR for an extended period (2,3). Patterns of kidney function trajectory in a given patient with CKD may have implications for clinical management (5). Furthermore, the risk factors associated with trajectory patterns may provide clues regarding the underlying pathophysiology of CKD progression.

Genetic factors may influence eGFR trajectory. The *APOL1* high–risk genotype, consisting of two copies of the G1 or G2 alleles, is associated with approximately twofold higher risk for CKD progression (6–9). This risk genotype has a population frequency of 13% in blacks and <1% in European Americans (10). The mechanism by which *APOL1* high–risk genotype affects CKD progression is still unclear, although environmental and genetic risk factors have been reported to act synergistically with the *APOL1*–associated renal susceptibility (11–14). Evaluating patterns of eGFR trajectory associated with *APOL1* risk status in patients with CKD may yield insight on *APOL1*–associated renal susceptibility. A steady decline trajectory may suggest an inevitable descent because of an ongoing pathophysiologic process, whereas an unsteady decline may reflect intermittent insults, such as AKI, contributing to CKD progression.

The African American Study of Kidney Disease and Hypertension (AASK) contributed to studies that established that participants with the *APOL1* high–risk genotype were two times as likely to experience CKD progression compared with those without the high-risk genotype (6,15). However, these studies did not assess the eGFR trajectory patterns associated with the *APOL1* high–risk genotype, an analysis that is possible in the AASK given its long–term follow-up (median of 9 years) and the frequent assessment of kidney function. We hypothesized that the AASK participants with the *APOL1* high–risk

genotype were more likely to experience a pattern of steady decline in eGFR.

Materials and Methods

Study Population and Design

The study design of the AASK has been reported previously (16,17). Briefly, the AASK had a randomized, controlled trial phase followed by a cohort phase. The randomized trial phase (1995–2001) enrolled 1094 patients ages 18–70 years old with self-reported race of black and CKD attributed to hypertension. In a 3×2 factorial design, participants were randomly assigned to one of three initial medications (ramipril, an angiotensin–converting enzyme inhibitor; metoprolol, a sustained release β-blocker; or amlodipine, a dihydropyridine calcium channel blocker) and one of two BP control targets: intensive control (goal of mean arterial pressure $\leq$92 mmHg) and standard control (goal of mean arterial pressure =102–107 mmHg). After the trial phase, patients who had not received a diagnosis of ESRD were invited to enroll in the cohort phase (April of 2002 through 2007), which provided BP management according to a standardized protocol on the basis of the results of the trial. Among all patients in the trial phase, 836 patients provided written informed consent for genetic studies. This study included 622 patients with the *APOL1* risk allele genotype data, $\geq$3 years of follow-up, and eight measures of eGFR for trajectory analysis. This work was approved by the Johns Hopkins Institutional Review Board.

Genotyping

ABI Taqman Assay was used to genotype the *APOL1* risk variants, G1 and G2. G1 consists of two missense single–nucleotide polymorphisms in high linkage disequilibrium on the same chromosome (rs73885319 and rs60910145) (7). G2 (rs71785313) is a two–amino acid deletion, which is in high linkage disequilibrium with G1 on the opposite chromosome. On the basis of the reported recessive inheritance mode of the *APOL1* risk variants (6), we defined the *APOL1* high–risk genotype as having two copies of the G1 or G2 alleles (G1/G1, G1/G2, or G2/G2).

Categories of eGFR Trajectory Patterns

Serum creatinine was measured twice at randomization (<3 months apart), at 3 and 6 months of follow-up, and then, every 6 months for the rest of the study. eGFR was calculated using the AASK estimating equation: $\text{eGFR}=329\times(\text{serum creatinine})^{-1.096}\times(\text{age})^{-0.294}\times(0.736$ for women). Probabilities of linearity and progression were estimated on the basis of the monthly slopes of eGFR trajectories approximated using a Bayesian smoothing technique (18). The details of algorithms for the estimation were reported previously (3). A brief description is available in Supplemental Material.

As shown in Figure 1, the probabilities of progression and linearity clustered on the two ends of the distribution. In other words, many participants had probabilities of progression or linearity close to 0% or 100%. Therefore, we dichotomized the probabilities at the median to create groups with approximately equal sizes and classified eGFR trajectory patterns into four categories: steady decline (probability of linearity $\geq$ median and probability of progression $\geq$ median), unsteady decline (probability of linearity $<$ median and probability of progression $\geq$ median), steady stable (probability of linearity $\geq$ median and probability of progression $<$ median), and unsteady stable (probability of linearity $<$ median and probability of progression $<$ median). The median was 75% for the probability of linearity and 78% for the probability of progression. Histograms of the probabilities of linearity and progression are presented in Figure 1. Random samples of the trajectories from the four categories are shown in Figure 2.

Analyses

We compared the baseline characteristics of participants by the four trajectory patterns using the chi-squared test for categorical variables, the Kruskal–Wallis test for skewed continuous variables, and linear regression for nonskewed

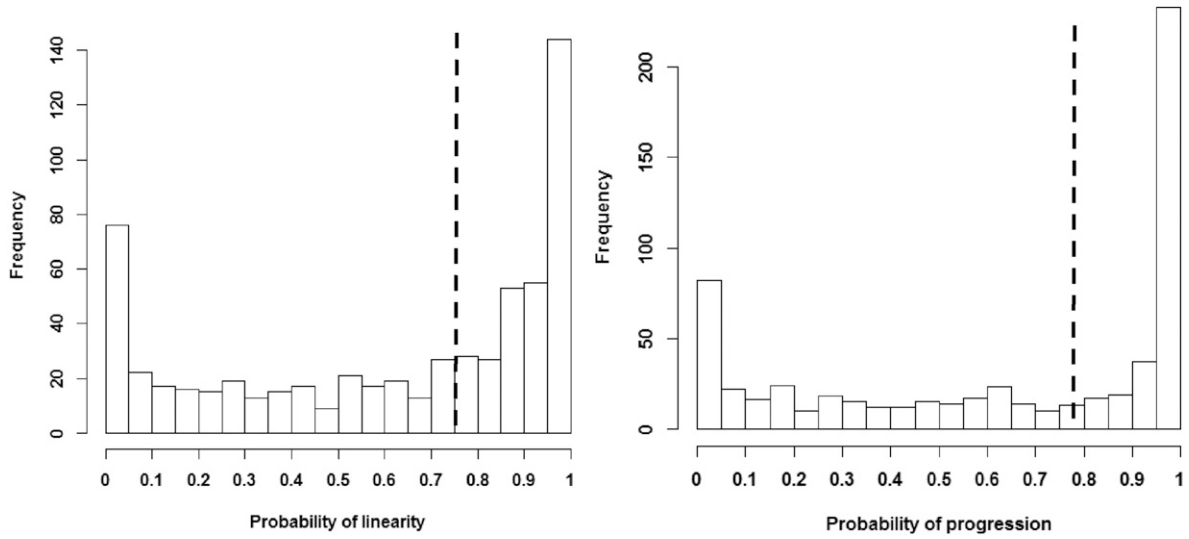

Figure 1. | **Histogram of the probabilities of linearity and progression.** The dashed line indicates the median.

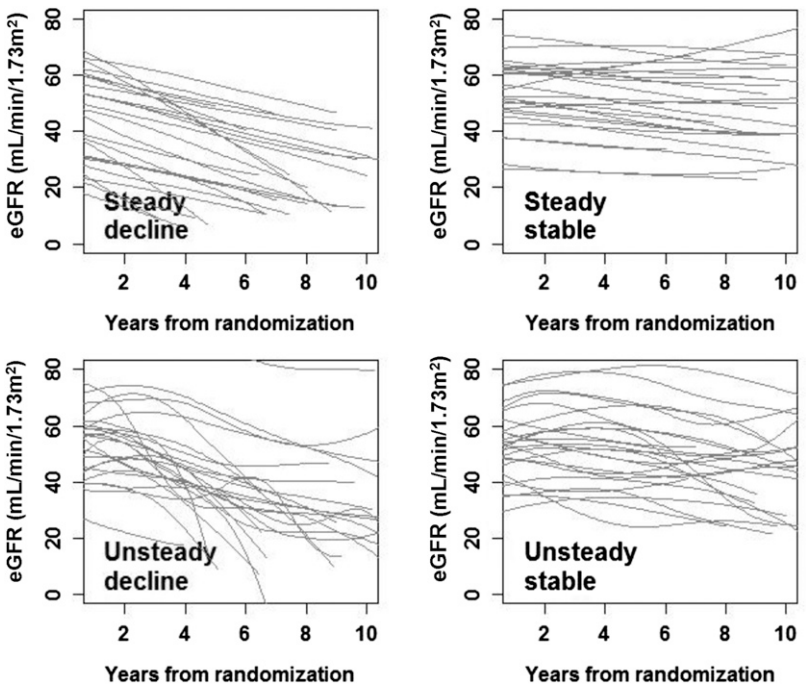

Figure 2. | **Random samples (*n*=25) of the trajectories from the four categories of eGFR trajectory patterns.**

continuous variables. To understand whether the inclusion criteria for this analysis differed between *APOL1* genotypes, we tested for the association between the *APOL1* high–risk status and the requirement criteria for eGFR trajectory pattern analysis (≥3 years of follow-up and eight measures of eGFR) using the chi-squared test. The association of *APOL1* high–risk status with the four eGFR trajectory patterns was evaluated using multinomial regression controlling for age at randomization, sex, drug treatment and BP target during the trial phrase, baseline clinical characteristics (eGFR, log–transformed urinary protein-to-creatinine ratio [UPCR], and diastolic BP), and follow-up time. Covariates were selected on the basis of literature review (3,19) or significant association with the trajectory categories in univariate analysis.

Because the pattern of steady decline in eGFR is our outcome of interest, in our primary analysis, we estimated the unadjusted and adjusted odds ratios (ORs) of the *APOL1* high–risk group for steady decline versus the other three trajectory patterns combined using logistic regression. We also evaluated whether the association between *APOL1* high–risk status and the steady decline pattern differed by baseline eGFR and UPCR levels. The covariates in logistic regression were the same as those used in multinomial regression. To evaluate whether the association between *APOL1* high–risk status and steady decline is sensitive to the cut point for categorizing the probabilities of linearity and progression, we conducted a sensitivity analysis using the 55th percentile of the two probabilities as a cut point. In addition, because participants with fewer measures of eGFR were more likely to have a linear trajectory, we also repeated the analysis including only participants with ≥12 measures of eGFR. To verify the recessive model of risk (which combines zero copies and one copy of the *APOL1* risk allele into a single risk group), we evaluated the association of the number of *APOL1* risk alleles with steady decline using logistic regression as well as the composite outcome of ESRD or doubling of serum creatinine using Cox regression. The covariates in this analysis were the same as those used in the primary analysis. Finally, we assessed whether the associations between the *APOL1* high–risk status and steady decline differ by baseline eGFR and proteinuria. Analysis of baseline characteristics was conducted using R. Other analyses were conducted using Stata 13.1 (StataCorp., College Station, TX).

Results

Overall, the percentages of participants in the four eGFR trajectory categories were 24.0% for steady decline, 25.9% for unsteady decline, 25.6% for steady stable, and 24.6% for unsteady stable (Table 1). Those experiencing steady decline were more likely to have lower diastolic BP, lower eGFR, higher proteinuria, and been assigned to the metoprolol treatment group and less likely to have been assigned to the amlodipine treatment group. Of the 622 participants, 22.0% had the *APOL1* high–risk genotype. This proportion was lower than that among the 71 participants not meeting criteria for inclusion in the eGFR trajectory pattern analysis (22.0% versus 32.4%; P=0.05) (Supplemental Table 1A). Similarly, the proportion of participants with the *APOL1* high–risk genotype was lower in the cohort phase than that in the trial phase (19.7% versus 35.1%; P<0.001) (Supplemental Table 1B). Among the four trajectory patterns, the steady decline trajectory pattern had the highest proportion of participants with the *APOL1* high–risk genotype (34.9% versus

Table 1. Characteristics of participants by eGFR trajectory category

Characteristic	Steady Decline, *n*=149	Unsteady Decline, *n*=161	Steady Stable, *n*=159	Unsteady Stable, *n*=153
Probability of linearity	≥Median	<Median	≥Median	<Median
Probability of progression	≥Median	≥Median	<Median	<Median
Percentage (*n*)	24.0 (149)	25.9 (161)	25.6 (159)	24.6 (153)
Age at randomization, yr, mean (SD)	54.4 (11.0)	52.5 (10.6)	56.0 (9.6)	54.5 (9.7)
Women, % (*n*)	45.0 (67)	38.5 (62)	45.3 (72)	35.3 (54)
Treatment drug, % (*n*)[a,b]				
Ramipril (ACE inhibitor)	44.3 (66)	39.8 (64)	47.2 (75)	39.2 (60)
Metoprolol (β-blocker)	47.0 (70)	34.8 (56)	37.1 (59)	39.2 (60)
Amlopdipine (calcium channel blocker)	8.7 (13)	25.4 (41)	15.7 (25)	21.6 (33)
BP target = standard, % (*n*)	49.0 (73)	49.7 (80)	52.2 (83)	53.6 (82)
Systolic BP, mean (SD)	149.7 (23.4)	153.1 (24.4)	148.3 (23.4)	147.9 (26.9)
Diastolic BP, mean (SD)[a]	93.7 (15.0)	97.8 (14.4)	95.2 (13.7)	95.7 (16.1)
eGFR, mean (SD)[a,b,c]	45.7 (14.3)	49.9 (13.7)	51.2 (12.8)	50.7 (12.2)
UPCR, mg/g, median (first, third quartiles)[a,b,c]	189 (52, 657)	99 (36, 294)	38 (21, 92)	40 (22, 97)
European ancestry percentage, median (first, third quartiles)[d]	0.12 (0.07, 0.21)	0.13 (0.08, 0.24)	0.12 (0.06, 0.24)	0.13 (0.07, 0.20)
Zero copies of *APOL1* risk alleles, % (*n*)	25.5 (38)	32.9 (53)	39.6 (63)	38.6 (59)
One copy of *APOL1* risk alleles, % (*n*)	39.6 (59)	41.6 (67)	45.3 (72)	48.4 (74)
Two copies of *APOL1* risk alleles, % (*n*)	34.9 (52)	25.5 (41)	15.1 (24)	13.1 (20)
Follow-up time, yr, median (first, third quartiles)[b,c]	8.1 (5.6, 9.5)	8.0 (5.7, 9.6)	9.9 (9.0, 10.8)	10.4 (9.0, 11.0)
No. of eGFR measures, median (first, third quartiles)[b,c]	18 (13, 22)	18 (14, 22)	22 (18, 24)	23 (19, 25)

Median (50th percentile) of the probability of linearity: 0.75. Median (50th percentile) of the probability of progression: 0.78.
ACE, angiotensin–converting enzyme inhibitor; UPCR, urine protein-to-creatinine ratio.
[a]*P* value <0.05 between steady decline and unsteady decline.
[b]*P* value <0.05 between steady decline and unsteady stable.
[c]*P* value <0.05 between steady decline and steady stable.
[d]The sample size for European ancestry percentage was 603.

25.5% in unsteady decline, 15.1% in steady stable, and 13.1% in unsteady stable). Participants with the steady decline trajectory had similar follow-up time as those with the unsteady decline trajectory and shorter follow-up time than those with the steady stable and unsteady stable trajectories.

In unadjusted analysis, the proportions of participants across all eight combinations of *APOL1* risk status and eGFR trajectory category were as follows: 8.4% with *APOL1* high–risk genotype and steady decline, 6.6% with *APOL1* high–risk genotype and unsteady decline, 3.9% with *APOL1* high–risk genotype and steady stable, 3.2% with *APOL1* high–risk genotype and unsteady stable, and 15.6%, 19.3%, 21.7%, and 21.4% in the corresponding trajectory groups with the *APOL1* low–risk genotype, respectively (Supplemental Table 2). In adjusted multinomial analysis, the adjusted percentage for those with the *APOL1* high–risk genotype and steady decline was 6.7%, 6.3% for unsteady decline, 4.9% for steady stable, and 4.1% for unsteady stable (Figure 3), whereas the adjusted percentage for those with the *APOL1* low–risk status and steady decline was 17.1%, 19.9% for unsteady decline, 20.6% for steady stable, and 20.3% for unsteady stable. The overall association between *APOL1* high–risk status and the four trajectory categories was statistically significant (unadjusted *P* value <0.001 and adjusted *P* value =0.05).

In the analysis using the steady decline trajectory pattern as the outcome, *APOL1* high–risk status was significantly associated with steady decline (unadjusted OR, 2.45; 95% confidence interval [95% CI], 1.62 to 3.69) (Table 2). This association attenuated but remained statistically significant after adjusting for demographic factors, baseline eGFR, UPCR, and treatment assignment (model 1: OR, 1.70; 95% CI, 1.08 to 2.68). This association remained similar after the addition of follow-up time as a covariate (model 2: OR, 1.59; 95% CI, 1.00 to 2.52). In the sensitivity analysis using the 55th percentile as the cut point for categorizing the eGFR trajectory patterns, the association between *APOL1* risk status and the steady decline trajectory pattern was slightly stronger (model 2: OR, 1.75; 95% CI, 1.07 to 2.87) (Supplemental Table 3).

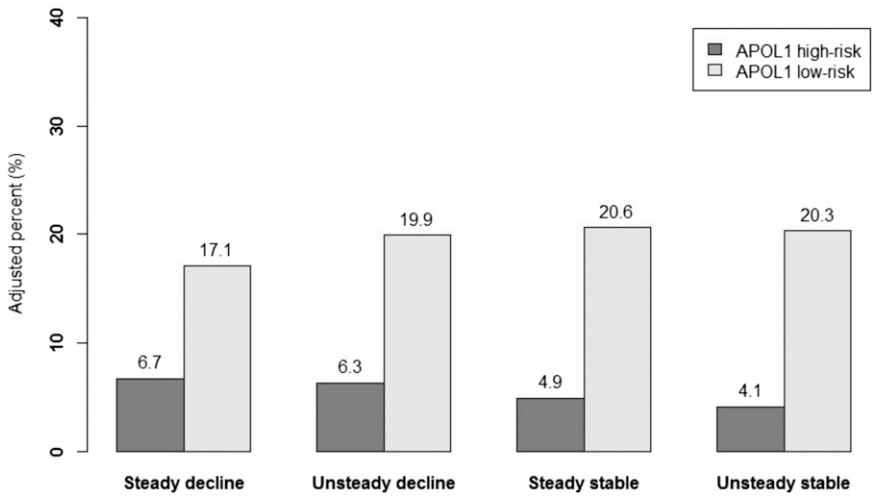

Figure 3. | **Adjusted percentage of participants by *APOL1* risk status and eGFR trajectory category.** Adjusted percentage total 100% across all eight combinations of *APOL1* risk status and eGFR trajectory category. Overall, 22% of the participants had the *APOL1* high–risk genotype, and 78% had the *APOL1* low–risk genotype. The adjusted percentages were estimated from multinomial regression using the four eGFR trajectory patterns as outcomes. Covariates included age at randomization, sex, randomized drug treatment group, randomized BP target, baseline eGFR, log(proteinuria), diastolic BP, and follow-up time for trajectory estimate.

Including only participants with ≥12 measures of eGFR also resulted in significant association between *APOL1* high–risk status and the steady decline trajectory pattern (model 2: OR, 1.67; 95% CI, 1.01 to 2.75).

The association between *APOL1* risk status and the steady decline pattern did not differ by baseline eGFR (*P* for interaction =0.42 between *APOL1* risk status and eGFR stratified at 45 ml/min per 1.73 m^2) and UPCR (*P* for interaction =0.55 between *APOL1* risk status and UPCR stratified at 0.22 g/g) (Table 2).

In sensitivity analysis that separated the low-risk status into zero or one *APOL1* risk allele, the unadjusted ORs for steady decline in those with two copies of the risk allele were significantly higher than in those with zero or one copy of the risk allele (two versus one copy: unadjusted OR, 2.82; 95% CI, 1.72 to 4.61; two versus one copy: OR, 2.21; 95% CI, 1.41 to 3.46) (Supplemental Table 4), whereas the ORs for steady decline were not significantly different between those with zero copies and those one copy of risk allele (one versus zero copies: unadjusted OR, 1.28; 95% CI, 0.81 to 2.01). In adjusted analysis, the ORs for steady decline in those with two copies of risk allele remained significantly higher than those with zero copies of the risk allele (two versus zero copies; model 2: OR, 1.97; 95% CI, 1.14 to 3.39) but were not significantly higher than those with one copy of the risk allele (two versus one copy; OR, 1.34; 95% CI, 0.81 to 2.23). Using ESRD or doubling of serum creatinine as outcome, the risk associated with two copies of the risk allele was significantly higher than that with zero or one copy of the risk allele in both unadjusted and adjusted analyses in this analyzed sample (Supplemental Table 5).

Table 2. Association between *APOL1* high–risk status and steady decline

Model	*APOL1* Low–Risk Group	*APOL1* High–Risk Group
N	485	137
Steady decline, %	20.0	40.0
Unadjusted, OR (95% CI)	1.00	2.45 (1.62 to 3.69)
Model 1, OR (95% CI)	1.00	1.70 (1.08 to 2.68)
Model 2, OR (95% CI)	1.00	1.59 (1.00 to 2.52)
Model 2 by subgroups, OR (95% CI)		
eGFR<45 ml/min per 1.73 m^2	1.00	2.12 (1.00 to 4.50)
eGFR≥45 ml/min per 1.73 m^2	1.00	1.46 (0.76 to 2.78)
UPCR<220 mg/g	1.00	1.40 (0.75 to 2.62)
UPCR≥220mg/g	1.00	1.68 (0.80 to 3.53)

Model 2 *P* for interaction between *APOL1* risk status and eGFR stratified at 45 ml/min per 1.73 m^2: 0.42. Model 2 *P* for interaction between *APOL1* risk status and UPCR stratified at 0.22 g/g: 0.55. Model 1 covariates included age at randomization, sex, randomized drug treatment group, randomized BP target, baseline eGFR, log(proteinuria), and diastolic BP. Model 2 added follow-up time for trajectory estimate. OR, odds ratio; 95% CI, 95% confidence interval; UPCR, urine protein-to-creatinine ratio.

Discussion

Main Finding

Among patients with CKD attributed to hypertension, those with the *APOL1* high–risk genotype were more likely to experience a steady decline in eGFR than those without the *APOL1* high–risk genotype.

In the Context of the Literature

Our study extends previous research that examines the relationship of *APOL1* risk variants with eGFR trajectory. The *APOL1* high–risk genotype has been associated with twofold higher risk for CKD progression (6,20), but eGFR trajectory pattern was not examined in these studies. In contrast, Li *et al.* (3) estimated the probability of linearity and progression of eGFR trajectories in the AASK and found that participants with lower eGFR and higher UPCR at baseline had higher probability of progression in univariate analysis; however, this study did not examine associations with *APOL1*. This study combined the estimated probabilities of progression and linearity to characterize the eGFR trajectory pattern associated with *APOL1* risk status. We found that the *APOL1* high–risk genotype was associated with a greater risk of steady decline, independent of baseline risk factors, compared with the *APOL1* low–risk variants. On the basis of previous findings, our primary analysis used the recessive genetic model, which combined participants with zero copies and participants with one copy of the *APOL1* risk variant into the low-risk group (6). This assumption of recessive genetic model was examined in sensitivity analysis using the number of risk variants as the predictor. The recessive genetic model held in unadjusted analysis using steady decline as the outcome and unadjusted and adjusted analyses using the composite outcome of ESRD or doubling of serum creatinine. Our sense is that the most appropriate model for *APOL1* risk variants is the recessive genetic model.

Although the mechanisms by which the *APOL1* risk variants influence kidney function remain unclear, these risk variants were reported to act synergistically with some environmental and genetic risk factors, such as higher levels of HIV viral load, hemostatic factors, and the glutathione-*S*-transferase-μ1 null allele, and independent of other risk factors of CKD progression, including smoking and net endogenous acid production (11–13,21). Our study found that, among patients with CKD attributed to hypertension, those with the *APOL1* high–risk genotype were more likely to experience a steady decline in eGFR. Importantly, this finding suggests that an ongoing, relentless CKD progression process may be more common among those patients with CKD with the *APOL1* high–risk genotype than those with the low–risk *APOL1* genotype. Additional work is warranted to unravel the pathophysiologic factors underlying this steady decline pattern.

Strengths of our study include the long duration of follow-up (median of 9 years) and the longitudinal eGFR measures that were obtained at frequent intervals (at least every 6 months).To our knowledge, no other study has such frequent measurement of eGFR over the long term. Furthermore, the association between *APOL1* risk status and the steady decline pattern was robust after excluding participants with <12 measures of eGFR. Our study also has limitations. The eGFR trajectory categories were on the basis of estimated probabilities, which included some level of uncertainty. However, the estimated trajectories smoothed out physiologic fluctuation in GFR and measurement errors in serum creatinine, the biomarker for GFR estimation. Therefore, the estimated probability of trajectory patterns reflect the sustained pattern of CKD progression. The percentage of participants with the *APOL1* high–risk genotype in this analyzed sample (22%) was higher than the frequency estimated from population-based cohorts (approximately 13%) (20,22). However, the participants excluded from the analysis of eGFR trajectory pattern because of the follow-up requirement (≥3 years of follow-up and eight measures of eGFR) had even higher proportions with the *APOL1* high–risk genotype (32%). This is likely because of the fact that those with the *APOL1* high–risk genotype had faster CKD progression to ESRD and thus, shorter follow-up. This exclusion might have led to underestimation of the association between the *APOL1* high–risk genotype and steady decline.

Among patients with CKD attributed to hypertension, those in the *APOL1* high–risk group were more likely to experience unremitting steady decline in eGFR than those in the low-risk group. These findings suggest that patients with the *APOL1* high–risk variants have an ongoing pathophysiologic process that perpetuates CKD progression.

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Disclosures

None.

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