CRP Polymorphisms and Progression of Chronic Kidney Disease in African Americans

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Background and objectives: Chronic inflammation may play a role in chronic kidney disease (CKD) progression. *CRP* gene polymorphisms are associated with serum C-reactive protein (CRP) concentrations. It is unknown if *CRP* polymorphisms are associated with CKD progression or modify the effectiveness of anti-hypertensive therapy in delaying CKD progression.

Design, setting, participants, & measurements: We genotyped 642 participants with CKD from the African American Study of Kidney Disease and Hypertension (AASK), selecting five tag polymorphisms: rs2808630, rs1205, rs3093066, rs1417938, and rs3093058. We compared the minor allele frequencies (MAF) of single nucleotide polymorphisms (SNPs) in AASK to MAFs of African Americans from NHANES III. Among AASK participants, we evaluated the association of SNPs with CRP levels and prospectively with a composite: halving the GFR, ESRD, or death.

Results: The MAF was higher for the *rs2808630_G* allele ($P = 0.03$) and lower for the *rs1205_A* allele ($P = 0.03$) in the AASK compared with NHANES III. Among AASK participants, the *rs3093058_T* allele predicted higher CRP concentrations ($P < 0.0001$) but not CKD progression. The rs2808630_GG genotype was associated with higher risk of the composite endpoint compared with the AA genotype ($P = 0.002$). Participants with the rs2808630_GG genotype on angiotensin converting enzyme inhibitors (ACEIs) *versus* β blockers had increased risk of progression ($P = 0.03$).

Conclusion: CRP SNPs that were associated with higher levels of CRP did not predict CKD progression. The rs2808630_GG genotype was associated with higher risk of CKD progression, and in patients with this genotype, ACEIs did not slow progression.

Clin J Am Soc Nephrol 5: 24–33, 2010. doi: 10.2215/CJN.01900309

Familial clustering of chronic kidney disease (CKD) and ESRD has been reported in populations throughout the world for most types of nephropathy (1–6). This genetic predisposition to ESRD seems to be strongly associated with race (7,8). Compared with people with no family history of kidney disease, African Americans with a first-degree relative with ESRD have a nine-fold increase in the risk of ESRD compared with a three- to five-fold increase in whites (8). Recently, the candidate gene *MYH9* has been identified as associated with nondiabetic ERSD in African Americans, and this association explains some of the disparity in incidence of ESRD observed between whites and African Americans (7,9). However, it is possible that additional genetic variants, such as those related to inflammatory pathways, may also be associated with ESRD.

Biomarkers of inflammation, including C-reactive protein (CRP), are increased even in early stages of CKD and have been linked to the risk of CKD progression (10–15). These observations have led to studies examining the genetic basis of inflammation and identification of several candidate genes for ESRD susceptibility (16–19). Recently, several large population-based studies showed that plasma CRP levels are under genetic influence (20–25). Some of these polymorphisms have been consistently associated with CRP levels (higher levels associated with rs3093058_T and lower levels associated with rs1205_A and rs2808630_G) and the risk of cardiovascular events (rs3093058_T) in African Americans (23).

CRP gene polymorphisms that affect CRP concentrations may reflect lifetime exposure to CRP more accurately than single time point measurements of serum CRP concentrations. The primary goal of this study was to characterize *CRP* gene polymorphisms and evaluate their association with CKD progression. We hypothesized that polymorphisms associated with higher levels of CRP would be associated with higher risk

Received March 18, 2009. Accepted September 23, 2009.

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/504–0024

of CKD progression. Additionally, we examined whether these polymorphisms modify the renoprotective effects of angiotensin converting enzyme inhibitors (ACEIs), a drug class known to have anti-inflammatory effects (26–28). We hypothesized that patients with polymorphisms associated with higher levels of CRP would benefit most from ACEIs.

Materials and Methods

Study Participants

This study included participants from the African-American Study of Kidney Disease and Hypertension (AASK) trial and The Third National Health and Nutrition Examination Survey (NHANES III). The AASK design and results have been previously described (9,29). Briefly, participants were self-identified African American, 18 to 70 yr, with hypertension defined by diastolic BP >95 mmHg and a GFR between 20 and 65 ml/min per 1.73 m^2, measured by I^{125} iothalamate clearance. Exclusion criteria included (*1*) identifiable cause of CKD other than hypertension; (*2*) diabetes mellitus (DM); (*3*) urine protein/creatinine ratio >2.5; (*4*) accelerated or malignant hypertension within 6 mo; (*5*) secondary hypertension, (*6*) serious illness; and (*7*) specific contraindication to a study drug. The protocol for genetic testing was approved by the institutional review board at each center, and written informed consent was obtained. Similarly, an Ethical Review Committee from the CDC was obtained for the NHANES III genetic information.

The AASK trial followed a 3 × 2 factorial design. Participants were randomized to β blockers (BBs; metoprolol 50 to 200 mg/d), calcium channel blockers (CCBs; amlodipine, 5 to 10 mg/d), or an ACEI (ramipril, 2.5 to 10 mg/d) and to two levels of BP: low (mean arterial pressure [MAP] goal of <92 mmHg) or usual (MAP 102 to 107 mmHg) (29). Data were collected for the following comorbidities: cancer, liver disease, congestive heart failure, left ventricular hypertrophy, arrhythmias, and cardiovascular disease. An interim analysis at 3 yr halted the amlodipine arm because patients with proteinuria (Upr/Cr > 0.22) taking amlodipine had faster GFR decline. DNA samples were available for 670 AASK participants that entered the trial. Serum CRP concentrations were measured in the AASK participants by nephelometry using a high-sensitivity assay (Dade Behring BN I). All measurements were done by a central laboratory at the Cleveland Clinic laboratory.

The NHANES are surveys conducted by the Centers for Disease Control to provide national estimates of the health of the U.S. civilian noninstitutionalized population. In the second phase of NHANES III conducted between 1991 and 1994, DNA samples were collected from 7159 consenting participants. We used genetic data from NHANES III participants that were self-identified African American, had GFR >60 ml/min, did not have DM, and had a UP/Cr ratio <2.5. For the NHANES III, we defined DM as self-reported physician diagnosis of DM, use of DM medications, fasting glucose >126 mg/dl, or a random glucose ≥200 mg/dl.

CRP Polymorphism Genotyping

Five tag single nucleotide polymorphisms (SNPs) were selected based on variation data for 23 European Americans and 24 African Americans resequenced by Seattle SNPs (pga.gs.washington.edu) (21,30) using LDSelect at default settings ($r^2 > 0.64$): rs1417938, rs1205, rs2808630, rs3093058, and rs3093066. We also selected rs1800947 given previous reports of its association with decreased CRP levels. Genotyping was performed using TaqMan Assays By Design (Applied Biosystems, Foster City, CA) under standard conditions. All markers had a 95% or higher genotyping efficiency.

Outcomes

The main outcome for the AASK and for this study was a composite endpoint of (*1*) GFR event defined as halving of the baseline GFR or a drop in the GFR ≥ 25 ml/min per 1.73 m^2, (*2*) ESRD, or (*3*) death. GFR was measured at baseline, at 3 mo, and every 6 mo thereafter. The follow-up of the trial ranged from 3.5 to 6.5 yr. Additionally, we compared at baseline the allele frequencies of each SNP in the AASK participants with those in the African Americans from the NHANES III with normal kidney function as described previously (21).

Statistical Analysis

All analyses were completed using SAS/Genetics 9.1 (SAS Institute, Cary, NC) and STATA 9 (College Station, TX). Each of the CRP SNPs was assessed to determine whether the observed genotype frequencies were in Hardy-Weinberg equilibrium. Marker-marker linkage disequilibrium was assessed using r^2, calculated for all pairwise SNP comparisons in the AASK dataset. We considered significance for a two-sided $\alpha = 0.05$ for all analyses and adjusted α α/n $0.05/11 = 0.0045$ after Bonferroni's correction for the number of genotype comparisons. CRP was log-transformed, and the distribution was checked for normality. Cox proportional hazards and Kaplan Meier plots were used to test the association between SNP and the composite outcome. Variables were selected *a priori* for the multivariate analysis. Haplotypes were inferred from tagSNPs using the expectation-maximization algorithm provided by SAS/Genetics 9.1, which also provides the probabilities for each individual's inferred haplotype pair for subsequent regression analyses. Common haplotypes (>5% frequency) were determined from the most likely pair of haplotypes inferred by the expectation-maximization algorithm. This study was an ancillary study to AASK, and as such, the analyses were not performed by the AASK Data Coordinating Center.

Results

Participant baseline characteristics are shown in Table 1. One hundred fifty-two individuals (24%) reached the composite endpoint: 109 experienced a GFR event, 80 reached ESRD, and 12 patients died.

CRP Allele and Genotype Frequencies

The observed genotype distribution for the six *CRP* SNPs was consistent with Hardy-Weinberg equilibrium. The allele frequencies for *CRP* SNPs in AASK and NHANES III cohorts are presented in Table 2. Participants in the AASK trial had a higher minor allele frequency (MAF) for rs2808630 (*G* allele: 17 *versus* 14% $P = 0.03$) and a lower MAF for rs1205 (*A* allele: 18 *versus* 21%, $P = 0.03$) compared with the African Americans from the NHANES III with normal kidney function, no DM, and a UP/Cr ratio <2.5; however, this association did not remain significant after adjusting for multiple comparisons (α/n $0.05/6 = 0.008$). AASK participants also had a higher MAF for rs3093058 (*T* allele: 19 *versus* 16%); however, this did not reach statistical significance ($P = 0.08$). Table 3 shows the genotype frequencies for each polymorphism for NHANES III and AASK participants.

CRP Genotypes and CRP Levels

The median CRP levels in the AASK cohort for the AA, AT, and TT rs3093058 genotypes were 0.40 (interquartile range [IQR] = 0.19, 0.81), 0.69 (IQR: 0.31, 1.13), and 1.14 mg/dl (IQR:

Table 1. Baseline characteristics of AASK participants

Characteristics	(n = 642)
Age (yr; mean ± SD)	54 ± 10.5
Gender (females)	41%
Serum creatinine [mg/dl; median (IQR)]	1.8 (1.5, 2.3)
Mean baseline GFR	47 ± 13.5
Systolic BP (mmHg; mean ± SD)	150 ± 24
MAP BP (mmHg; mean ± SD)	114 ± 16.1
Diastolic BP (mmHg; mean ± SD)	96 ± 14
Urine protein/creatinine ratio (mean ± SD)	0.31 ± 0.50
Mean urine 24-h proteinuria (mean ± SD)	0.50 ± 0.94
Body mass index (mean ± SD)	31.1 ± 6.7
Current smokers	28% (n = 180)
CRP, [mg/dl; median (IQR)]	0.5 (0.21, 0.93)
Incident ESRD	12% (n = 80)
Number of patients halving the GFR	17% (n = 109)
Death	1.8% (n = 12)
Combined endpoint	24% (n = 152)
Mean rate of decline ml/min per 1.73 m^2	−1.9 (−0.39, −3.5)
Blood pressure assignment	Low: 50.15% (n = 322); Usual: 49.9% (n = 320)
Drug assignment	
ACE inhibitor	41% (n = 265) Low BP: 52%(n = 138)/Usual BP: 48%(n = 127)
β blocker	39% (n = 252) Low BP: 50%(n = 125)/Usual BP: 50%(n = 127)
Calcium channel blockers	19% (n = 125) Low BP: 47%(n = 59)/Usual BP: 53%(n = 66)

Table 2. CRP SNP allele frequencies for African Americans from NHANES III and AASK participants

CRP SNPs	Location	Alleles	Allele Frequencies		P Value[a]
			NHANES III (n = 450)	AASK (n = 642)	
rs2808630	3′-flanking region	A	86%	83%	0.03[b]
		G	14%	17%	
rs1205	3′-flanking region	A	21%	18%	0.03[b]
		G	79%	82%	
rs3093066	5′-flanking region	A	24%	22%	0.3
		C	76%	78%	
rs1417938	Intron 1	A	87%	88%	0.3
		T	13%	12%	
rs3093058	5′-flanking region	A	84%	81%	0.08
		T	16%	19%	
rs1800947[c]	Exon 2	C	1%	1%	0.6
		G	99%	99%	

[a]Unadjusted for multiple comparisons.
[b]Not statistically significance at an α = 0.008 level after applying a Bonferroni correction ($\alpha = n/6$).
[c]Data for rs1800947 are for all NHANES III African-Americans participants with DNA (n = 2108) because the data user agreement does not allow outputs with counts less than 5.

0.45, 1.81), respectively. The rs3093058 genotypes AT and TT were associated with significantly higher levels of CRP in the AASK cohort ($P < 0.001$) compared with the AA genotypes (Table 4). The P value remained significant after Bonferroni's correction for 11 comparisons. No other tested *CRP* polymorphism was associated with CRP levels.

Table 3. Genotype in NHANES III and AASK participants for each of the CRP polymorphisms

	Genotype Frequency (%)																	
	rs2808630			rs1205			rs3093066			rs1417938			rs3093058			rs1800947[a]		
	AA	AG	GG	GG	AG	AA	CC	AC	AA	AA	AT	TT	AA	AT	TT	GG	CG	CC
NHANES	74	24	2	62	33	4	58	36	6	76	23	2	71	27	3	98	2	0
AASK	69	28	3	67	30	3	61	17	5	77	21	1	66	31	4	98	2	0

[a]Data for rs1800947 are for all NHANES III African-Americans participants with DNA (n = 2108) beause the data user agreement does not allow outputs with counts less than 5.

Table 4. Association between serum CRP levels and CRP SNPs in the AASK participants

CRP SNPs and Genotypes	*N*	CRP Level Median (IQR)	β Coefficient (95% CI) Log CRP	*P* Value[a]
rs2808630				
AA	439	0.51 (0.23, 0.95)	Ref	
AG	192	0.44 (0.19, 0.92)	−0.17 (−0.37, 0.02)	0.08
GG	16	0.34 (0.09, .43)	−0.21 (−0.77, 0.35)	0.46
rs1205				
GG	447	0.52 (0.23, 0.96)	Ref	
AG	179	0.44 (0.21, 0.83)	−0.11 (−0.30, 0.09)	0.27
AA	25	0.06 (−0.42, 0.54)	−0.06 (−0.42, 0.54)	0.81
rs3093066				
CC	399	0.52 (0.23, 0.95)	Ref	
AC	213	0.40 ((0.20, 0.90)	−0.20 (−0.39, −0.01)	0.04
AA	37	0.66 (0.24, 1.01)	−0.04 (−0.34, 0.43)	0.82
rs1417938				
AA	503	0.51 (0.22, 0.94)	Ref	
AT	141	0.43 (0.23, 0.85)	−0.02 (−0.23, 0.19)	0.85
TT	6	0.55 (0.38, 1.22)	0.49 (−0.38, 1.4)	0.27
rs3093058				
AA	423	0.40 (0.19, 0.81)	Ref	
AT	204	0.69 (0.31, .13)	0.40 (0.21, 0.59)	<0.001[b]
TT	20	1.14 (0.45, 1.81)	0.86 (0.37, 1.37)	<0.001[b]
rs1800947				
GG	644	0.5 (0.22, 0.92)	Ref	
CG	7	0.21 (0.12, 0.74)	−0.50 (−1.31, 0.30)	0.22
CC	NA	NA	NA	NA

NA, not applicable.
[a]Unadjusted for multiple comparisons.
[b]Statistical significance at an α = 0.0045 after Bonferroni correction for 11 genotypes.

CRP Genotypes and Clinical Outcomes

Among AASK participants, the rs2808630_GG genotype was associated with an increased risk of reaching the composite endpoint (adjusted hazard ratio [HR], 3.62; 95% confidence interval [CI], 1.62 to 8.23; P = 0.002) compared with the AA genotype (Table 5; Figure 1). The P value remained significant after Bonferroni's correction for 11 comparisons (adjusted significance level α/n 0.05/11 = 0.0045). Potential confounding variables were determined *a priori*, including age, gender, comorbidities, BP treatment assignment, baseline GFR, proteinuria, body mass index, smoking, and CRP levels. None of the other tested polymorphisms were associated with the composite endpoint. There were no statistically significant differences in the demographic or clinical characteristics among the different rs2808630 genotypes (Table 6). Other independent predictors for the composite endpoint in the model for the SNP rs2808630 included ACEI use, smoking, baseline proteinuria, and baseline GFR (Table 7).

CRP Levels and Clinical Outcomes

The median CRP in the AASK participants involved in this study was 0.50 mg/dl (IQR, 0.22, 0.93). The median CRP levels were higher in women compared with men (0.60 *versus* 0.41 mg/dl, $P < 0.0001$), consistent with observations in the general

Table 5. Association of CRP polymorphisms and renal outcomes

CRP SNPs and Genotype	*N*	Composite of Halving Your GFR, Reaching ESRD, or Death	
		Hazard Ratio (95% CI)	*P* Values[a]
rs2808630			
AA	439	Ref	
AG	191	0.87 (0.59–1.29)	0.49
GG	15	3.65 (1.62–8.23)	0.002[b]
rs1205			
GG	447	Ref	
AG	179	1.14 (0.74–1.52)	0.48
AA	25	0.90 (0.36–2.27)	0.84
ss3093066			
CC	399	Ref	
AC	213	1.02 (0.6–1.5)	0.89
AA	37	1.23 (0.6–2.5)	0.56
rs1417938			
AA	503	Ref	
AT	141	0.89 (0.58–1.37)	0.62
TT	6	1.07 (0.14–7.89)	0.94
rs3093058			
AA	423	Ref	
AT	204	0.81 (0.55–1.19)	0.28
TT	20	0.92 (0.28–3.02)	0.89
rs1800947			
GG	644	Ref	
CG	7	0.19 (0.03–1.14)	0.11
CC	NA	NA	

Composite outcome = decrease in GFR by 50% or a drop in the GFR ≥25 ml/min per 1.73 m^2, ESRD, or death.

Hazard ratios are adjusted for age, gender, BP treatment assignment, drug treatment assignment, body mass index, baseline GFR, baseline proteinuria, smoking, and number of comorbidities.

Ref, reference group homozygous for the major allele; NA, not applicable.

[a]Unadjusted for multiple comparisons.

[b]Statistical significance at an α=0.0045 after Bonferroni correction for 11 genotypes.

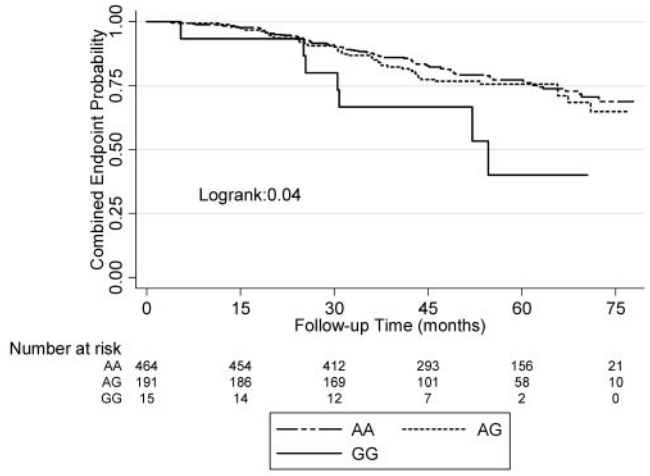

Figure 1. Survival without experiencing the combined endpoint of halving the GFR. ESRD or death in CKD patients with different genotypes of the rs2808630.

population (31). In this study, CRP level did not predict CKD progression as reflected by the combined endpoint (HR, 0.94; 95% CI, 0.80 to 1.10; $P = 0.4$).

CRP Genotypes and ACEI Use

Pharmacogenomic analysis was performed to evaluate the effect of ACE inhibition within each rs2808630 genotype. There was no statistical difference between the three drugs and their effect on the composite outcome. We restricted our analyses to individuals with UP/Cr >0.22 based on the findings from the original trial in which the benefit of ACEI was the strongest in this group (9,29). Patients randomized to ACEI therapy in the setting of a baseline UP/Cr >0.22 experienced fewer composite endpoints than those assigned to CCBs (46 *versus* 54%; HR, 0.53; 95% CI, 0.31 to 0.91; $P = 0.02$) and not significantly different than those assigned to BBs (46 *versus* 51%; HR, 0.89; 95% CI, 0.57 to 1.30; $P = 0.6$). For the most common genotype, rs2808630 AA with UP/Cr >0.22 ($n = 128$), ACEI therapy was superior to CCBs (HR, 0.33; 95% CI, 0.17 to 0.67; $P = 0.002$) and similar to BBs (HR, 1.35; 95% CI, 0.75 to 2.43; $P = 0.3$; Figure 2A). For all

Table 6. Clinical Characteristics of AASK participants by rs2808630 genotypes

	Rs2808630 Genotypes			*P* Value
	GG	AG	AA	
N	15	191	436	
Age (yr)	48.42 ± 12.55	54.7 ± 9.86	53.82 ± 10.70	0.23
Gender (% male)	40%	59%	60%	0.3
Serum creatinine (mg/dl)	1.8 (1.4, 2.1)	1.8 (1.5, 2.4)	1.8 (1.5, 2.3)	0.79
C-reactive protein, mg/dl, median (IQR) (*P* for log CRP)	0.34 (0.09, 1.43)	0.44 (0.19, 0.92)	0.51 (0.23, 0.95)	0.54
Mean baseline GFR	46 11.01	45.4 13.25	47.49 13.65	0.53
Years with hypertension	13.2 ± 8.73	13.9 ± 9.47	14.2 ± 9.9	0.67
24-h urine protein at baseline (g/d)	0.44 ± 0.73	0.54 ± 0.53	0.48 ± 0.92	0.4
Systolic BP at randomization (mmHg)	149.4 ± 23.36	150.5 ± 25.23	150.2 ± 23.7	0.5
Diastolic BP at randomization (mmHg)	100 ± 16	95.4 ± 14	96 ± 14.4	0.09
History of heart disease	40%	50%	50%	0.74
Body mass index (kg/m^2)	33.93 ± 6.4	30.5 ± 6.7	31.3 ± 6.64	0.09
Number of comorbidities	0 (0,1)	1 (0,1)	1 (0,1)	0.09
Smoking	6 (40%)	56 (29%)	186 (27%)	0.58
GFR slope (ml/min per m^2)	−3.03 IQR −5.2, −0.22	−2.18 IQR: −3.6, −0.26	−1.87 IQR: −3.3, −0.26	0.07

Table 7. Multivariate Cox proportional hazards analysis of association of the rs2808630 genotypes and composite outcomes and other clinical predictors

Variable	Hazard Ratio (95% CI)	*P* Value[a]
Genotype		
rs2808630_AA	Ref	
rs2808630_AG	0.87 (0.59, 1.29)	0.49
rs2808630_GG	3.65 (1.62, 8.23)	0.002[b]
BP assignment[c]	0.78 (0.55, 1.12)	0.19
Drug assignment		
Calcium channel blockers	Ref	
β blockers	0.72 (0.44, 1.17)	0.19
ACE inhibitors	0.56 (0.34, 0.91)	0.02
Log CRP (mg/dl)	0.96 (0.81, 1.14)	0.65
Age	1.01 (0.99, 1.02)	0.53
Gender[d]	1.04 (0.71, 1.52)	0.83
Body mass index (kg/m^2)	0.98 (0.95, 1.02)	0.32
Mean baseline GFR (ml/min)	0.96 (0.94, 0.97)	<0.0001
Urine protein (g/d)	1.88 (1.64, 2.17)	<0.0001
Number of comorbidities	1.04 (0.85, 1.26)	0.72
Smoking (current *versus* never or former)	1.63 (1.11, 2.40)	0.01

Adjustement done for baseline covariates.
BP assignment: usual: MAP 102–107 mmgh; low: MAP <92 mmgh.
Mean baseline GFR: the mean of two GFR measurements by isothalamate.
[a]Unadjusted for multiple comparisons.
[b]Statistical significance at an $\alpha = 0.0045$ after Bonferroni correction for 11 genotypes.
[c]Reference group low BP.
[d]Reference group male.

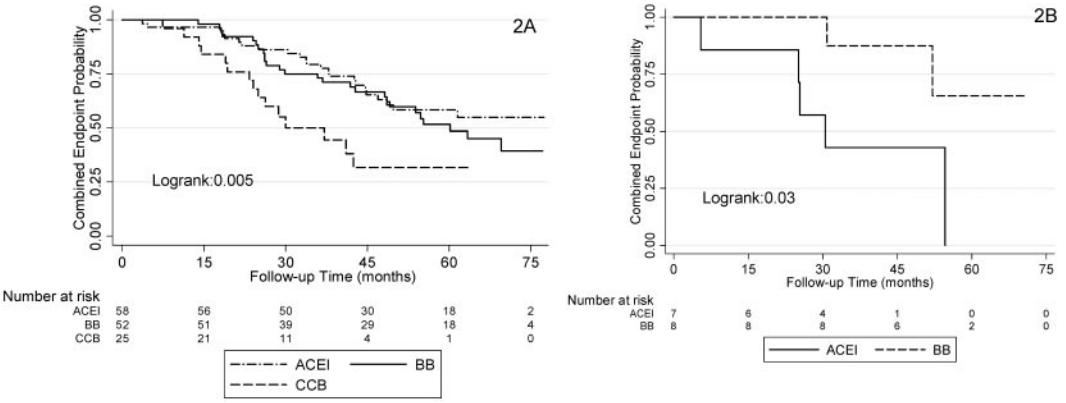

Figure 2. Effect of different antihypertensive agents in meeting the composite endpoint for participants homozygous for the major allel rs2808630AA and baseline urinary protein-to-creatinine ratio (UP/Cr) >0.22 (above, panel 2A) and for participants homozygous for the minor allele rs2808630CC (below, panel 2B).

individuals with the rs2808630_GG genotype ($n = 15$), those allocated to ACEI therapy had a higher rate of progression than those allocated to BBs (HR, 5.34; 95% CI, 1.00 to 28.3; $P = 0.04$; Figure 2B). We were unable to divide the rs2808630_GG genotype by protein excretion because of the small number of individuals with UP/Cr >0.22 and the genotype of interest ($n = 6$). There was statistical evidence to support effect modification by an interaction between ACEI and rs2808630 genotype and the composite outcome (P for the interaction = 0.007).

Haplotype Analyses, CRP Levels, and Clinical Outcomes

Six common haplotypes were inferred from six *CRP* tagSNPs in the AASK participants (Table 8). The rs1800947 SNP was dropped from the model because of the low MAF (<1%). We tested for an association between CRP levels and *CRP* haplotypes, and the results of the haplotype-based analyses mimic the single SNP analyses. The haplotype tagged by the *T* allele of rs3093058 (H2) was associated with higher levels of CRP ($P < 0.0001$). No CRP haplotype was associated with the composite endpoint.

Discussion

The primary goal of this study was to evaluate the role of *CRP* polymorphisms in CKD progression. AASK represents an ideal population to study these associations because CKD progression occurs four times faster in African Americans (32). Although our study suggests that some common mechanisms/genetic susceptibilities to ESRD may share a common pathway, it is important to acknowledge that distinct renal diseases may involve other independent factors. Our study is performed in a cohort of African Americans with hypertensive kidney disease. Our results showed that *CRP* SNP rs3093058 was associated with increased levels of CRP in the CKD population (TT *versus* AT and AA genotypes) and is consistent with what has been shown in the general population (20–24).

Although the frequency of the rs3093058 *T* allele, which is associated with increased CRP levels, was marginally higher in the AASK population than community controls, this was not statistically significant. More importantly, we found no association between this allele and CKD progression. On the other hand, we showed a strong association between the rs2808630_GG genotype, which has been associated with lower levels of CRP (21,22), and both baseline CKD (higher in AASK than in controls) and CKD progression, as reflected by the composite endpoint. Additionally, we showed that individuals with this genotype assigned to ACEI progressed faster than those assigned to BBs.

Table 8. Association between CRP haplotypes and plasma CRP concentration

Haplotype	Allele						Estimated Frequency (%)	Log CRP	
	rs1800947 G/C	rs2808630 A/G	rs1205 G/A	rs3093066 C/A	rs1417938 A/T	rs3093058 A/T		β-Coefficient	*P* Value
H1		A	G	A	A	A	22.2%	−0.73	0.2
H2		A	G	C	A	T	18.7%	0.44	<0.0001
H3		A	A	C	A	A	17.8%	−0.07	0.4
H4		G	G	C	A	A	17.2%	−0.14	0.1
H5		A	G	C	A	A	12.5%	−0.14	0.2
H6		A	G	C	T	A	11.7%	−0.01	0.8

Haplotypes with estimated frequency of <5% were excluded from analysis.

The lack of association observed between the *T* allele of the rs3093058, which tags a promoter variation rs3093062 (20,21), and CKD progression could be explained by a lack of statistical power to detect the small increase in risk of CKD in African Americans. Alternatively, it is possible that rs3093058 is not a key pathogenic mediator for CKD in this population. Although epidemiologic data support the role of inflammation, including CRP in the pathogenic process (11,13–15), CRP is a surrogate marker of the inflammatory process (33). CKD patients have a high burden of comorbidities, and reverse causation may explain the associations with CRP. However, studies of non-*CRP* inflammatory cytokine gene polymorphisms could provide a link between inflammatory genes and pathways with CKD.

The underlying mechanisms regarding the association between the GG genotype of the rs2808630 and the composite endpoint in this study remains unclear. Despite adjustment for multiple comparisons, it is possible that this association represents a false-positive finding. A potential explanation is that the GG genotype of the rs2808630 is in linkage disequilibrium with another functional SNP associated with ESRD not genotyped directly in our study. Using the Genome Variation Server (gvs.gs.washington.edu/GVS/), we surveyed a 50-kb region surrounding rs2808630 for SNPs in high linkage disequilibrium with the rs2808630 in the West African samples from the International HapMap Project (34). No SNP was in high linkage disequilibrium (defined as $r^2 > 0.80$), and 12 intergenic SNPs were in moderate linkage disequilibrium (defined at $r^2 > 0.50$). Fine mapping and functional studies will be needed to identify the causal SNP underlying the association described here.

It is possible that rs2808630 is the causal SNP and affects the response to reno-protective interventions. Our hypothesis was that individuals with chronic inflammation will benefit the most from ACEIs (26–28,35). Albeit small sample size, individuals with the most common genotype AA and UP/Cr ratio >0.22 benefited from ACEIs. Individuals with the less common genotype, GG (low inflammatory profile), were at an increased risk for the primary endpoint even when allocated to ACEIs compared with BBs (9). These findings should be considered preliminary and need to be confirmed in larger studies.

The main strength of our study is that it was performed in an randomized controlled trial primarily designed to address CKD progression, and therefore, outcome ascertainment was optimal. GFR, for example, was performed using the gold standard iothalamate clearance. Also, the longitudinal nature of the study allowed us to evaluate the genotype effect in disease progression among high-risk patients with CKD stages 3 and 4.

Our study is not without limitations. First, our study results are limited to African Americans with hypertensive CKD and cannot be extrapolated to other populations or other diseases. In addition, neither the AASK nor the NHANES III dataset currently has ancestry informative markers to adjust for admixture. Our main focus is CKD progression within the AASK cohort, which was a multicenter study across the nation, and ancestry background should be similar. However, admixture markers will need to be performed in the AASK cohort for future comparisons with other populations.

Finally, a limitation of our study is the lack of replication for the association of CRP polymorphisms and CKD progression in other independent cohorts. However, our study represents an independent replication for the association of CRP polymorphisms with CRP levels (21,22,24). Independent replication studies in racially diverse CKD progression cohorts will be necessary to substantiate the new findings.

In conclusion, CRP SNPs that are associated with higher levels of CRP were more common in African Americans with hypertensive CKD than in African Americans without CKD; however, these SNPs were not associated with CKD progression. Additionally, we showed an association between the rs2808630_GG genotype (low inflammatory profile) with both baseline CKD and the risk of CKD progression and potential loss of renal benefit from ACEIs. Larger studies in African Americans are needed to further explore the role of CRP polymorphisms in response to ACEI and CKD progression.

Acknowledgments

We thank C. L. Sanders (currently with Medco Health) and J. McLean from the NCHS at the CDC for assistance with the NHANES III genetic data. This work was supported in part by Clinical Translational Science Award 1UL-1RR024975 from the National Center for Research Resources. The Vanderbilt University Center for Human Genetics Research, Computational Genomics Core provided computational and/or analytical support for this work. All genotyping was performed by the Vanderbilt DNA Resources Core. A.M.H. was supported by a Research Career Development Award and a Clinical Research Center of Excellence from the Department of Veterans Affairs, National Kidney Foundation (NKF) Young Investigator Award and DK077373. K.C. is supported by K23-DK080952–01 and an NKF Young Investigator Award. M.S.L. was supported by Grants DK048689, DK057867, and RR000071. T.A.I. is supported in part by Grants DK62849, AT003844, HL065193, and DK082192.

Disclosures

None.

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