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Apolipoprotein L1 gene variants associate with prevalent kidney but not prevalent cardiovascular disease in the Systolic Blood Pressure Intervention Trial

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Apolipoprotein L1 gene (*APOL1*) G1 and G2 coding variants are strongly associated with chronic kidney disease (CKD) in African Americans (AAs). Here *APOL1* association was tested with baseline estimated glomerular filtration rate (eGFR), urine albumin:creatinine ratio (UACR), and prevalent cardiovascular disease (CVD) in 2571 AAs from the Systolic Blood Pressure Intervention Trial (SPRINT), a trial assessing effects of systolic blood pressure reduction on renal and CVD outcomes. Logistic regression models that adjusted for potentially important confounders tested for association between *APOL1* risk variants and baseline clinical CVD (myocardial infarction, coronary, or carotid artery revascularization) and CKD (eGFR under 60 ml/min per 1.73 m^2 and/or UACR over 30 mg/g). AA SPRINT participants were 45.3% female with a mean (median) age of 64.3 (63) years, mean arterial pressure 100.7 (100) mm Hg, eGFR 76.3 (77.1) ml/min per 1.73 m^2, and UACR 49.9 (9.2) mg/g, and 8.2% had clinical CVD. *APOL1* (recessive inheritance) was positively associated with CKD (odds ratio 1.37, 95% confidence interval 1.08–1.73) and log UACR estimated slope (β) 0.33) and negatively associated with eGFR (β −3.58), all significant. *APOL1* risk variants were not significantly associated with prevalent CVD (1.02, 0.82–1.27). Thus, SPRINT data show that *APOL1* risk variants are associated with mild CKD but not with prevalent CVD in AAs with a UACR under 1000 mg/g.

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There has been significant progress in the delineation of the spectrum of nondiabetic chronic kidney diseases (CKDs) in African Americans (AAs) that are associated with the apolipoprotein L1 gene (*APOL1*) G1 and G2 coding variants. Patients with *APOL1*-associated primary glomerulosclerosis often have proteinuria, secondary hypertension, focal segmental glomerulosclerosis, HIV-associated nephropathy (focal segmental glomerulosclerosis, collapsing variant), focal global glomerulosclerosis accompanied by interstitial and vascular changes (often labeled 'hypertension-attributed' nephropathy), sickle cell nephropathy, or severe lupus nephritis on kidney biopsy.[1–6] Patients inheriting two *APOL1* risk variants have high rates of progression to end-stage kidney disease (ESKD), explaining a large fraction of the differential risk of ESKD in AAs.[6–8] However, the specific disease mechanisms remain unclear. Modifying genetic (*APOL1* by second gene) and environmental factors (*APOL1* by environmental exposure) are likely present and may account for the variable glomerular histologic lesions.[3,9–12] Weaker *APOL1* association is observed with albuminuria and reduced kidney function in population-based studies of AAs.[13–15]

Recent results from the Jackson Heart Study (JHS) and Women's Health Initiative (WHI) reported an association between *APOL1* nephropathy variants and incident cardiovascular disease (CVD).[16] This finding warrants additional consideration, as the African American Study of Kidney Disease and Hypertension (AASK) did not detect a significant relationship between *APOL1* and participant survival.[8] AASK extended *APOL1* association to AAs with putative hypertension-attributed nephropathy and urine protein:creatinine ratios (UPCRs) <2500 mg/g,[7] but did not appear to support *APOL1* association with CVD.[8] AASK also demonstrated that, although aggressive blood pressure control slowed nephropathy progression in participants who had proteinuria exceeding 300 mg/day, the overall response to renin–angiotensin system blockade was poor and nearly 60% of AASK participants met a primary study end point (mainly nephropathy progression, not death) within 10 years.[17] *APOL1* was significantly associated with CKD in AASK cases and only the *APOL1* genotype predicted nephropathy progression; blood pressure treatment arm and medication class did not.[7] Therefore, AASK suggested that *APOL1* is primarily involved in the progression of nondiabetic nephropathy, without independent effects on CVD. As such, it is unclear why JHS and WHI results differed from those of AASK. Approximately one-quarter of JHS and WHI participants had diabetes mellitus, a known CVD risk factor, and their CVD definition differed from those employed in the National Institutes of Health (NIH)-sponsored AASK and Systolic Blood Pressure Intervention Trial (SPRINT).[16] AASK also excluded subjects with diabetes mellitus, congestive heart failure (CHF), or heart block greater than first degree.[18] Thus, analysis of other large cohorts is important to define potential relationships between *APOL1* and CVD.

The present analyses assessed *APOL1* G1 and G2 risk variant association with prevalent CVD and baseline CKD, estimated glomerular filtration rate (eGFR), and albuminuria in AAs at high risk for CVD in SPRINT.[19] SPRINT enrolled large numbers of nondiabetic individuals with hypertension; participants included those with CVD and associated risk factors, the elderly, and those with nephropathy having low levels of albuminuria.

RESULTS

Among all 2802 AAs enrolled in SPRINT, 2571 (91.8%) consented to participate in genetic research studies and had baseline clinical and *APOL1* G1 and G2 genotype data that passed quality control analyses. In the multivariate analysis, 342 of 2802 participants were excluded because of failure to provide consent for genetic analyses, lack of DNA, or missing covariates. Compared with those in the multivariate analysis, no significant differences were observed for excluded participants regarding age, sex, body mass index (BMI), number of blood pressure medications, or CVD events, although higher mean ± s.d. (median) eGFR 79.0 ± 21.0 (78.6) ml/min per 1.73 m^2 ($P = 0.03$) and a trend toward lower urine albumin:creatinine ratio (UACR) 25.5 ± 56.9 (8.1) mg/g ($P = 0.0501$) were present (Supplementary Table S1 contains characteristics of participants included and excluded from the multivariate analysis).

Individuals in this analysis were 45.3% female with mean ± s.d. (median) age of 64.3 ± 9.3 (63) years, mean arterial pressure 100.7 ± 12.2 (100) mm Hg, CKD-epidemiology (EPI)-eGFR 76.3 ± 22.9 (77.1) ml/min per 1.73 m^2, and UACR 49.9 ± 188.6 (9.2) mg/g; 16.2% had CVD defined by the SPRINT Manual Of Operations (see Materials and Methods), whereas 8.2% had clinical CVD defined as prior coronary or carotid artery revascularization (surgical or percutaneous) or myocardial infarction (MI). Table 1 summarizes the demographic and clinical differences between those individuals with zero or one copy and those with two copies of the *APOL1* G1/G2 risk alleles. Briefly, those with two-risk variants were 1 year younger, but otherwise these two groups had similar proportions of women and similar BMI, tobacco use, and fasting glucose levels. Individuals with two copies of the *APOL1* risk variants had higher African ancestry (82 vs. 78%, $P = 4.2 \times 10^{-9}$) and albuminuria ($P = 3.8 \times 10^{-6}$) and more advanced kidney disease (serum creatinine concentration $P = 0.0091$; eGFR $P = 0.0249$; CKD prevalence $P = 0.0129$), even after adjusting for multiple comparisons.[20] In contrast to CKD, Table 1 reveals the general absence of *APOL1* association with baseline measures of CVD, whether defined as in the SPRINT Manual Of Operations or as clinical CVD (MI, coronary, or carotid artery revascularization).

In order to account for the potentially confounding effects of age, gender, renin–angiotensin system blockade, and African ancestral proportion on risk for kidney disease, multiple regression models that adjusted for these *a priori* factors as covariates were computed (Table 2). In the multiple logistic model, individuals with two copies of the G1/G2 risk variants had a higher prevalence of CKD (odds ratio (OR) = 1.37, $P = 0.0095$), had lower eGFR (slope $(\hat{\beta}) = -3.57$, $P = 0.0029$), and higher levels of albuminuria (log(UACR), slope $(\hat{\beta}) = 0.33$, $P = 7.67 \times 10^{-6}$), compared with those with zero- or one-risk variants. Comparable effect sizes were observed if the sample was restricted to >0.40 and >0.80 African ancestry (data not shown).

A similar multiple logistic regression approach was computed to test for an association between *APOL1* risk variants and clinical CVD (Table 3). Specifically, a logistic regression model was computed with prevalent CVD as the response and adjusting for an *a priori* list of CVD risk factors (that is, age, gender, BMI, number of blood pressure medications, statin use, eGFR, UACR, and smoking) and African ancestral proportion as covariates. As with the univariate analysis in Table 1, the adjusted analyses in Table 3 show no evidence of an association between the number of *APOL1* risk variants (additive genetic model) and clinical CVD ($P = 0.86$, OR 1.02, 95% CI (confidence interval) 0.82–1.27). Adjusting for the same list of covariates but testing for an *APOL1* association under a recessive model yielded comparable results ($P = 0.54$). The number of blood pressure medications, use of statins, and smoking were significantly associated with clinical CVD. Given the lack of association with *APOL1*, it is