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Sickle cell trait is not independently associated with susceptibility to end-stage renal disease in African Americans

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Abstract

Conflicting reports exist as to whether sickle cell trait is a risk factor for the progression of nephropathy. In order to determine whether African Americans with sickle cell trait are at increased risk for kidney disease, we assessed the genetic association between sickle cell trait and end-stage renal disease (ESRD). Hemoglobin S, non-muscle myosin heavy chain 9 (*MYH9*), and apolipoprotein L1 (*APOL1*) risk variants were genotyped in 3258 unrelated African Americans: 1085 with non-diabetic ESRD, 996 with type 2 diabetes-associated ESRD, and 1177 controls. Since *APOL1* is strongly associated with ESRD in African Americans, interactions between *APOL1* and *MYH9* risk variants and hemoglobin S were assessed using case-only and case-control centered two-way logistic regression interaction analyses. The sickle cell trait genotype frequencies were 8.7% in non-diabetic ESRD, 7.1% in type 2 diabetes-ESRD, and 7.2% in controls. There was no age-, gender-, and admixture-adjusted significance for sickle cell trait association with non-diabetic ESRD (odds ratio 1.16); type 2 diabetes-ESRD (odds ratio 1.01); or all-cause ESRD (combined non-diabetic and type 2 diabetic-ESRD patients compared to the controls; odds ratio 1.05) in dominant models. In addition, no evidence of *APOL1* or *MYH9* interactions with sickle cell trait was detected. Hence, sickle cell trait is not associated with diabetic or non-diabetic ESRD in a large sample of African Americans.

Keywords

African American; *APOL1*; diabetes; end-stage kidney disease; hemoglobin S; hypertension

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DISCLOSURE

All the authors declared no competing interests.

Individuals homozygous for the sickle (S) variant of hemoglobin (Hb) A develop sickle cell disease, manifested by anemia, recurrent pain crises, chronic kidney disease, stroke, vascular occlusion, pulmonary disease, infectious complications, and premature mortality.[1] Renal manifestations in sickle cell disease may include loss of urinary concentrating ability, papillary necrosis, glomerular lesions, including focal segmental glomerulosclerosis (FSGS), interstitial scarring, and iron deposition.[2] Sickle cell trait has been associated with papillary necrosis, hematuria, and urinary concentrating defects.[3] There have been conflicting reports as to whether sickle cell trait is a risk factor for the development of diabetic nephropathy.[4–6] A recent report described a high prevalence of sickle cell trait (heterozygous carriers; HbAS) among African American end-stage renal disease (ESRD) patients, suggesting an increased risk for individuals with HbAS.[7] Replication analyses in larger samples have yet to be performed.

The HbAS genotype is present in approximately 7–9% of African Americans, with higher frequencies in younger individuals.[8,9] HbS was selected for in Africa because of the protection it affords from malarial infection, a scenario similar to the protection from trypanosomal infection provided by heterozygosity for apolipoprotein L1 (*APOL1*) nephropathy risk variants (G1: non-synonymous coding variant 342G:384M and G2: 6 bp deletion).[10,11] Whereas *APOL1* contributes to nephropathy risk in an autosomal recessive inheritance pattern, HbS reportedly had a dominant effect on risk,[7] with sickle cell trait being associated with ESRD.

We tested for a genetic association between the single-nucleotide polymorphism encoding HbS and ESRD in African Americans residing in the southeastern United States to determine whether the HbAS genotype was associated with commonly reported etiologies of ESRD. Cases with ESRD attributed to type 2 diabetes mellitus (T2D) and non-diabetes mellitus (non-DM) causes, predominantly ‘hypertension-attributed’ and glomerular disease associated, were evaluated. In addition, relationships between *APOL1* G1/G2 nephropathy risk variants and *non-muscle myosin heavy chain 9* gene (*MYH9*) risk variants (E1 risk haplotype)[12–14] and HbS were assessed to determine whether interactions between these genes were present.

RESULTS

Analyses were performed in 1085 unrelated African American cases with nondiabetic etiologies of ESRD, 996 cases with T2D–ESRD, and 1177 non-nephropathy controls (413 with T2D). Table 1 contains demographic data from these 3258 individuals. Although controls were younger than ESRD cases, they were older than the mean age at onset of T2D and ESRD in the T2D–ESRD and non-DM ESRD cases, respectively. Relative to the non-nephropathy controls, ESRD cases had significantly higher percentages of African ancestry (Table 1; P-value $=8.8 \times 10^{-8}$). Individual African ancestry proportion data were used as covariates in the program SNPGWA version 4.0 (http://www.phs.wfubmc.edu/public/bios/gene/downloads.cfm) to calculate genotypic association.

Table 2 displays HbAS genotype frequencies and Hardy–Weinberg equilibrium results in the cases and controls. HbS met Hardy–Weinberg equilibrium expectations in all groups with a genotype frequency of 7.2% in controls, 8.7% in non-DM ESRD cases, and 7.1% in T2D–ESRD cases. Table 2 reveals the African ancestry-adjusted association results for HbS in non-DM ESRD cases, T2D–ESRD cases, and all-cause (combined) ESRD cases, relative to non-nephropathy controls. Significant evidence of association was not detected in age, gender, and ancestry-adjusted analyses in cases with non-DM ESRD (odds ratio (OR) 1.16; 95% confidence interval (CI) 0.85–1.60; P =0.34, dominant model), cases with T2D–ESRD

(OR 1.01; 95% CI 0.70–1.50; P =0.96, dominant model), or all-cause (combined) ESRD cases (OR 1.05; 95% CI 0.79–1.40; P =0.74, dominant model). Additional analyses were performed by comparing the 1085 non-DM ESRD cases with the 704 nondiabetic controls and the 996 T2D–ESRD cases with the 413 T2D controls, and no evidence of association with HbAS was detected (data not shown). When including diabetes duration as a covariate in the model, results were unchanged and HbAS was not associated with T2D–ESRD (OR 1.13; 95% CI 0.68–1.67; P =0.63).

Age, gender, and African ancestry-adjusted *APOL1* association testing revealed an OR =4.45 for association in all ESRD cases (recessive model, 95% CI 3.60–5.49; P =9.24E^{-44}). Table 3 contains the results of interaction analyses between HbAS and *APOL1*, and HbAS with *MYH9* nephropathy risk variants employing both the powerful case-only method, as well as the case–control two-way interaction method. Because of low counts of HbS homozygotes, only the dominant model had sufficient power for analysis. As shown, there was no interaction between HbS and the *MYH9* E1 risk haplotype or *APOL1* G1 and G2 alleles.

DISCUSSION

The current report tested for genetic association between sickle cell trait and common complex forms of ESRD in African Americans. No evidence of association between HbAS and either diabetic or nondiabetic etiologies of ESRD was detected in this large sample of African Americans from the southeastern United States. In addition, no evidence of an interaction was seen between chromosome 22q nephropathy risk variants in *APOL1* or *MYH9* and HbS. Patients with sickle cell disease are known to develop renal abnormalities, including risk for ESRD requiring renal replacement therapy. Our results stand in contrast to a series of 188 patients with ESRD reported by Derebail *et al.*[7] In that series, almost 15% of ESRD cases had sickle cell trait as determined by high-performance liquid chromatography. We performed direct genotyping in 2081 African Americans with ESRD. In addition, interaction analyses were performed in this report as chromosome 22q nephropathy risk variants predispose to FSGS and focal global glomerulosclerosis in African Americans, lesions that are reported to occur in higher frequency in patients with sickle cell disease.[2] FSGS and focal global glomerulosclerosis are now known to comprise the vast majority of cases with non-DM ESRD in African Americans.[10,11,15]

Strengths of the current report include the large sample size, direct genotyping for HbS, and adjustment for overall percentage of African ancestry, age, and gender. Moreover, potential gene–gene interactions were assessed between HbS and powerful renal disease polymorphisms in the *APOL1* and *MYH9* genes. Individuals with HbAS genotypes have a normal lifespan and are typically unaffected unless exposed to low oxygen tension (high altitude) or high oxygen demand. *APOL1* and HbS both appear to have been selected for in Africa on the basis of the protection they afford from malaria and trypanosomal infection, respectively. However, this analysis suggests that *APOL1* and HbS both appear to be associated with susceptibility to nephropathy in autosomal recessive patterns, with no evidence of risk for nephropathy in individuals heterozygous for risk variants (e.g., those with sickle cell trait). Additional evidence from our group supports the lack of an effect of sickle cell trait on development of subclinical nephropathy in African Americans with diabetes mellitus.[5] The cohort studied by Bleyer *et al.*[5] was limited to individuals with diabetes mellitus who underwent determinations of estimated glomerular filtration rates with simultaneous glycated hemoglobin testing during outpatient clinic visits at Wake Forest Baptist Medical Center; they were not enriched for ESRD. None of those individuals were cases or controls in this report. Therefore, the current results in cases with severe nephropathy (ESRD) are consistent with those in subclinical nephropathy.

One must be careful to evaluate for any potential bias that could occur and affect the study results. The cases were recruited from dialysis centers throughout the southeastern United States. A bias would be whether patients with sickle cell trait preferentially underwent kidney transplantation or whether individuals with sickle cell trait would be less likely to participate in our study. It is interesting to note that many individuals do not realize that they have sickle cell trait,[16] and testing for sickle cell trait is not routinely done in ESRD patients. This would reduce the chance of bias. The prevalence of sickle cell trait in the control population was similar in our study and that of Derebail *et al*.[7] Controls in their report were derived from North Carolina live-birth screenings for African Americans. The North Carolina State Laboratory provided de-identified results for all live births identified as African American for counties in which University of North Carolina dialysis populations were based. However, the prevalence of sickle cell trait was 15% in their ESRD population compared with 8% in the current study population. Although a different methodology was used to determine the presence of sickle cell trait, this is unlikely to have led to the differences in our findings. The present study was much larger and encompassed a larger geographical area. A potential study limitation is the possibility that small numbers of controls with chronic kidney disease could have been included; this would reduce the likelihood of detecting association (although no trend was observed). Shorter T2D durations in diabetic controls relative to T2D–ESRD cases could also influence results, although adjusting for diabetes duration did not change the results. It is difficult to identify large numbers of African Americans with long durations of diabetes lacking microalbuminuria because of their high prevalence of nephropathy. In addition, subjects with DM may develop progressive chronic kidney disease in the absence of proteinuria. Finally, although logistic regression does not address the possibility that sickle trait may affect nephropathy progression rates, we feel that these data and the report by Bleyer *et al*.[5] make this less likely.

Association studies with multivariable adjustment may miss differences that can be revealed with stratified analyses. Although stratification provides the strongest protection against confounding, it can also reduce power. We compared the distribution of the two continuous covariates used in these analyses by sickle trait status. The mean (s.d.) of age and admixture was 56.8 years (13.9) and 0.80% (0.1) in the sickle trait group and 55.7 years (12.9) and 0.78% (0.1) in the non-sickle trait group. The Wilcoxon two-sample *P*-value was 0.19 for age and 0.003 for admixture; 53% of sickle trait carriers were women as were 55% of the noncarriers ($P = 0.59$). As admixture was associated with sickle trait status, we adjusted for it to prevent confounding. Approximately 7–9% of African Americans possess one copy of HbS.[8,9] Our report evaluated prevalent dialysis patients and similarly aged controls born in the southeastern United States. Similar frequencies of HbS were observed in cases and controls, although this sample consisted of middle-aged and older participants. Our results neither support higher risk for ESRD in HbS carriers nor a survival bias whereby HbS carriers live longer than noncarriers. There is no *a priori* evidence that heterozygous carriers of HbS manifest improved survival and would therefore be more likely to survive to initiate dialysis. We further note that the strong *APOL1* genetic association initially observed with FSGS was easily detectable in prevalent dialysis patients with all-cause ESRD from this report.

In contrast to an earlier, smaller report, we conclude that African Americans who have a single copy of the *HbS* gene are not at increased risk for developing nondiabetic or diabetic ESRD (or subclinical nephropathy), relative to unaffected individuals. In addition, nephropathy risk variants in *APOL1* function independently from HbS when contributing to nondiabetic ESRD.

MATERIALS AND METHODS

Patient populations

Diagnostic criteria for African American participants in on-going genetic analyses of T2D- and non-T2D-associated ESRD at Wake Forest School of Medicine have been reported.[14,17,18] Briefly, self-described African Americans born in North Carolina, South Carolina, Georgia, Virginia, or Tennessee formed the study population. Peripheral blood specimens for DNA extraction were collected from unrelated prevalent dialysis patients who reportedly had ESRD attributed to hypertension, glomerular disease, or T2D. Cases were diagnosed as having hypertension-attributed ESRD by virtue of high blood pressure preceding initiation of renal replacement therapy with hypertensive target-organ damage (retinopathy or left ventricular hypertrophy) and low-level proteinuria (≤30 mg/dl on urine dipstick, <0.5 g protein/24 h on timed urine collection, or urine protein:creatinine ratio <0.5 g/g) or in the absence of proteinuria measurements. In the presence of renal biopsy evidence of a primary glomerular disease (e.g., FSGS), proteinuria ≥0.5 g/24 h or ≥100 mg/dl on urinalysis, nondiabetic subjects were diagnosed as having chronic glomerular disease-associated ESRD. T2D-associated ESRD was diagnosed in patients with diabetes developing after the age of 25 years, with renal histological evidence of diabetic nephropathy or diabetes durations ≥5 years before initiating renal replacement therapy in the presence of diabetic retinopathy and/or proteinuria >500 mg/24 h, or with >5 years diabetes duration before ESRD in the absence of other known causes of kidney disease. Individuals with cystic renal diseases, hereditary nephritis, or urological causes of ESRD were excluded.

The control group was recruited from the same geographical region as ESRD cases. Nondiabetic controls included 780 individuals without nephropathy identified at primary care medicine clinics, community health fairs, and community screenings. Because of their low risk for developing nephropathy, serum creatinine concentrations were not uniformly measured in nondiabetic controls. However, in a subset of 602 of these controls, 98.4% were found to have serum creatinine concentrations ≤1.5 mg/dl in men and ≤1.3 mg/dl in women (the 16 controls with elevated serum creatinine concentrations were excluded from analysis). Additional controls with T2D included 413 African American-Diabetes Heart Study participants, all with serum creatinine concentrations ≤1.5 mg/dl in men and ≤1.3 mg/dl in women, and a spot urine albumin:creatinine ratio <30 mg/g.[19] Although a small number of controls may have chronic kidney disease, these criteria make it unlikely that many had estimated glomerular filtration rates below 60 ml/min. All cases and controls provided written informed consent, and the study was approved by the Institutional Review Board at the Wake Forest School of Medicine.

Genotyping

DNA extraction from whole blood was performed using the PureGene system (Gentra Systems, Minneapolis, MN). The HbS single-nucleotide polymorphism (rs334) was genotyped using the iPLEX Sequenom MassARRAY platform (San Diego, CA). Seventy diallelic ancestry informative markers were genotyped to determine whether population substructure biased our results.[20] The 44 Yoruba (YRI), 39 European American controls, 1177 African American controls, and 2081 African American ESRD samples were genotyped using Custom Genotyping Services (Illumina, San Diego, CA) or Sequenom MassArray. Genotyping efficiency was >98.4%, and 104 blind duplicates were included to ensure genotyping accuracy.

Statistical analyses

HbS allele frequency differences between the case and control groups were analyzed using logistic regression multivariable models adjusting for admixture, age, and gender under a

dominant genetic model. SNPGWA version 4.0 was used to calculate genotypic association adjusted for African ancestry proportions. FRAPPE (Frequentist Estimation of Individual Ancestry Proportion) was used to calculate African ancestry proportions in the case and control population.[20]

An interaction term between HbS and (a) *MYH9* risk variants or (b) *APOL1* risk variants was fitted in the logistic regression model to assess whether the OR of HbS varied significantly with risk status for *MYH9* or *APOL1*. *MYH9* 'risk' was defined as homozygosity for the E1 haplotype.[12–14] *APOL1* 'risk' was defined as two copies of the G1 or G2 risk alleles.[10] To improve power to detect small-effect gene–gene interactions, case-only analyses were performed to evaluate potential interactions between HbS and *MYH9* or *APOL1*.[21] As *APOL1* and *MYH9* both reside on chromosome 22, a chromosome different from HbS, the assumption of independence between the genes holds using this approach.

P-values, ORs, and 95% CIs were calculated to assess the relationship between HbS and ESRD, as well as interactions between HbS and the chromosome 22 nephropathy risk variants. The interaction analyses were performed using SAS software (version 8.2; SAS Institute, Cary, NC), and hypothesis tests were two-sided and considered statistically significant at $P<0.05$.

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Table 1

Demographic data in ESRD cases and non-nephropathy controls

Group	*N*	Female (%)	Mean±s.d., age (years)	Mean±s.d., BMI (kg/m^2)	African ancestry (%)	Mean±s.d., age at ESRD (years)	Mean±s.d., age at T2D (years)
Non-DM ESRD cases	1085	44.3	53.9 (±14.6)	27.1 (±6.9)	79.5 (±10.3)	48.4 (±15.5)	NA
T2D ESRD cases	996	60.0	61.6 (±10.4)	29.8 (±7.2)	78.7 (±11.4)	58.0 (±11.0)	41.5 (±12.4)
Non-nephropathy controls	1177	57.1	51.9 (±11.2)	32.1 (±13.1)	76.9 (±11.2)	NA	45.7 (±10.1)[a]

Abbreviations: BMI, body mass index; DM, diabetes mellitus; ESRD, end-stage renal disease; NA, not applicable; T2D, type 2 diabetes mellitus.

[a]Subset of 413 controls with T2D.

Mean (s.d.) DM duration: 19.9 (10.7) years in T2D ESRD cases; 9.4 (7.9) years in non-nephropathy controls with T2D.

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Table 2

Genotypic association for HbS in ESRD cases with controls, adjusted for admixture, age, and gender

Group	Sample size	HbAS genotype frequency	HWE controls	HWE cases	*P*-value, dominant	OR (CI)	*P*-value, additive	OR (CI)
Non-DM ESRD	1085	0.087	0.619	0.406	0.3446	1.16 (0.85–1.6)	0.3402	1.18 (0.86–1.6)
T2D–ESRD	996	0.071	0.619	0.237	0.9617	1.01 (0.70–1.5)	0.9945	1.00 (0.70–1.4)
Combined all-cause ESRD	2081	0.079	0.619	0.171	0.7398	1.05 (0.79–1.4)	0.7436	1.05 (0.79–1.4)
Controls	1177	0.072	0.619	NA	NA	NA	NA	NA

Abbreviations: CI, 95% confidence interval; DM, diabetes mellitus; HbS, hemoglobin S; HbAS, sickle cell trait (heterozygous carriers); HWE, Hardy–Weinberg equilibrium; ESRD, end-stage renal disease; NA, not applicable; OR, odds ratio; T2D, type 2 diabetes mellitus.

Table 3

HbS–chromosome 22 nephropathy variant interaction analyses

Analysis type	Non-DM ESRD	T2D-ESRD	All-cause ESRD
MYH9– E1 interaction	*P*-value (*N*)	*P*-value (*N*)	*P*-value (*N*)
Case only	0.99 (case, *N*=1007)	0.23 (case, *N*=938)	0.39 (case, *N*=1945)
Case–control two-way interaction	0.46 (case, *N*=1007; control, *N*=1098)	0.36 (case, *N*=938; control, *N*=1098)	0.92 (case, *N*=1945; control, *N*=1098)
APOL1–G1/G2 interaction			
Case only	0.82 (case, *N*=1024)	0.28 (case, *N*=968)	0.30 (case, *N*=1992)
Case–control two-way interaction	0.1 (case, *N*=1024; control, *N*=1089)	0.68 (case, *N*=968; control, *N*=1089)	0.25 (case, *N*=1992; control, *N*=1089)

Abbreviations: APOL1, apolipoprotein L1; DM, diabetes mellitus; ESRD, end-stage renal disease; HbS, hemoglobin S; MYH9, non-muscle myosin heavy chain 9; SNP, single-nucleotide polymorphism; T2D, type 2 diabetes mellitus.

Case-only association and case–control centered two-way interaction tests were conducted using a logistic regression model with age, gender, and admixture adjustment. As the main effect of SNP (rs334 HbS) had a minor allele frequency of ~0.04, the counts of samples homozygous for the minor allele were too small to have sufficient power in additive or recessive models. Therefore, only the dominant model was examined and results are presented.