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# The association of the *MYH9* gene and kidney outcomes in American Indians: the Strong Heart Family Study

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## Abstract

Chronic kidney disease (CKD) is an important public health problem in American Indian populations. Recent research has identified associations of polymorphisms in the myosin heavy chain type II isoform A (*MYH9*) gene with hypertensive CKD in African-Americans. Whether these associations are also present among American Indian individuals is unknown. To evaluate the role of genetic polymorphisms in the *MYH9* gene on kidney disease in American Indians, we genotyped 25 SNPs in the *MYH9* gene region in 1,119 comparatively unrelated individuals. Four SNPs failed, and one SNP was monomorphic. We inferred haplotypes using seven SNPs within the region of the previously described E haplotype using Phase v2.1. We studied the association between 20 *MYH9* SNPs with kidney function (estimated glomerular filtration rate, eGFR) and CKD (eGFR < 60 ml/min/1.73 $m^2$ or renal replacement therapy or kidney transplant) using age-, sex- and center-adjusted models and measured genotyped within the variance component models. *MYH9* SNPs were not significantly associated with kidney traits in additive or recessive genetic adjusted models. *MYH9* haplotypes were also not significantly associated with kidney outcomes. In conclusion, common variants in *MYH9* polymorphisms may not confer an increased risk of CKD in American Indian populations. Identification of the actual functional genetic variation responsible for the associations seen in African-Americans will likely help to clarify the lack of replication of this gene in our population of American Indians.

## Introduction

Chronic kidney disease (CKD) is highly prevalent in American Indians and contributes to increased burden of disease in this population (Narva 2003). Among American Indian and Alaskan Native participants in the Kidney Early Evaluation Program (2000–2006), 29% had either reduced kidney function or microalbuminuria (Jolly et al. 2009). In the Strong Heart Study (SHS), increased urine albumin excretion was observed in 20–48% of the American Indian participants (Robbins et al. 1996), and it was associated with older age, type 2 diabetes (which is highly prevalent at ~53%), hypertension and percentage of Indian blood. American Indians have twice the risk of end-stage renal disease (ESRD) compared to individuals of European ancestry (2009; Scavini et al. 2007) with a younger median age of incident ESRD (57.6 years) than African-American individuals (58.9 years) and Whites (67.1 years) (2009).

Recent research has linked genetic variation in the myosin heavy chain type II isoform A (*MYH9*) gene to hypertensive ESRD and focal segmental glomerulosclerosis (FSGS), the most common glomerulonephritis associated with ESRD (Kao et al. 2008; Kopp et al. 2008). These studies used admixture models, which rely on alleles that differ in frequency across populations of different ancestry and are suitable to the study of diseases, such as CKD, with large disparities among racial/ethnic groups. Among individuals primarily of African descent, several single nucleotide polymorphisms (SNPs) in the *MYH9* gene were associated with FSGS (odds ratio, OR = 5.0, 95% confidence interval, CI = 3.5–7.1 for haplotype E-1) and with non-diabetic ESRD (OR = 2.2, 95% CI = 1.5–3.4) (Kopp et al. 2008). These findings have been replicated in a large sample of African-Americans with ESRD attributed to hypertension (Freedman et al. 2009b) and for albuminuria in African-American participants of the HyperGEN study (Freedman et al. 2009c). The at risk *MYH9* haplotype E-1 (comprising three SNPs in intron 23 and rs3752462) is less often observed in individuals of European descent (Kopp et al. 2008). Whether the *MYH9* gene is also associated with CKD among American Indian individuals is unknown.

In this study, we genotyped multiple SNPs in the *MYH9* gene and studied the association of these genetic variants with kidney function (eGFR) and albuminuria in a large sample of American Indian participants of the Strong Heart Family Study.

## Methods

### Population and phenotypes

The National Heart, Lung, and Blood Institute (NHLBI) funded the Strong Heart Family Study (SHFS) beginning in 1998 to study the genetics of cardiovascular disease among American Indian populations (North et al. 2003). The SHFS recruited members of 94 large, multigenerational families (mean family size 40 individuals, range 5–110) from the original cohort of participants of the Strong Heart Study. Over 3,800 American Indians aged 14–93 years from 13 tribes located in Arizona, North and South Dakota, and Oklahoma were examined. The SHFS protocols were approved by the Indian Health Service Institutional Review Board, by the Institutional Review Boards of the participating Institutions, and by the Indian tribes participating in these studies (Lee et al. 1990; North et al. 2003). All participants gave informed consent for genetic testing. For this study, a sample of comparatively unrelated individuals [with 753 half-sib relative pairs (kinship coefficients of 0.25) and 2,891 of first cousin relationship or less (kinship coefficients ≤0.125) among them] were genotyped ($N$ = 1,119).

Socio-demographic data and medical history were obtained by a personal interview during a clinical exam. Self-reported Indian heritage was obtained by asking the percentage of Indian blood. Forearm resting blood pressure was measured three consecutive times by a trained person using a mercury column sphygmomanometer (WA Baum Co) and size-specific cuffs after 5 min of resting. The first and fifth Korotkoff sounds were recorded. The average of the last two measures was used for all analyses. Hypertension was defined by a systolic BP ≥140 or diastolic BP ≥90 or use of antihypertensive drugs (Chobanian et al. 2003). Anthropometric measures of body weight (kg) and height (m) were used to estimate body mass index (BMI, $kg/m^2$). Type 2 diabetes was defined as a fasting blood glucose of 126 mg/dl or higher, history of diabetes or use of diabetic medications (1997). Impaired glucose-tolerance was defined by the World Health Organization criteria and was based on fasting plasma glucose and 75-g oral glucose-tolerance test results.

Albumin and creatinine were measured in a random urine sample using nephelometric immunochemistry and alkaline picrate methods, respectively. Urinary albumin excretion was estimated by the albumin to creatinine ratio (ACR, mg/g). Serum creatinine was measured in fasting samples by the picric acid method in the MedStar Research Institute (Washington, DC). Glomerular filtration rate (eGFR) was estimated using the abbreviated Modification in Diet in Renal Diseases (MDRD) equation: eGFR (ml/min/1.73 $m^2$) = 186.3 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.210 if African-American) (Levey et al. 1999). This equation has been previously validated in an American Indian population (Perkins et al. 2005). eGFR values higher than 200 were set to 200 ml/min per 1.73 $m^2$ ($N$ = 2) and those less than 15 ml/min per 1.73 $m^2$ were set to 15 ($N$ = 17). CKD was defined by an eGFR of 60 ml/min/1.73 $m^2$ or lower, a history of dialysis or kidney transplant. Urine ACR categories were defined by <30 mg/g versus ≥30 mg/g urine creatinine.

### Genotyping

Twenty-five SNPs were selected in the *MYH9* region based on polymorphisms in HapMap Asian and Caucasian (CEU) populations and if they were available in the Illumina platform. We used this strategy for two primary reasons. First, there is a paucity of published data on SNP and haplotype variation in American Indians, specifically for this gene. Second, while we

could have chosen to select tag SNPs using the Caucasian or Asian HapMap samples, a recent study using HapMap data to capture patterns of variation in populations not represented in the HapMap (Conrad et al. 2006) demonstrated that American Indian population, represented by the Pima Indians, had only 60–70% tag portability with HapMap Han Chinese and Japanese combined samples. However, the portability of these samples to American Indians represented in our study is unknown. The SNPs were genotyped in 1,119 individuals by inclusion in an Illumina iSelect Custom 12-Sample BeadChip using the Infinium II Assay. The assays were performed according to the manufacturer's protocol (Illumina, San Diego, CA, USA), and alleles were detected and analyzed using the Illumina BeadArray Reader and Bead-Studio software. Replica samples were included as controls. Four SNPs failed the assay (rs136187, rs9610489, rs2413398, and rs1557540) and one SNP was monomorphic (rs735854). All remaining SNPs had a call rate >95%.

### Haplotypes

Of four SNPs that have defined the E haplotype (at risk haplotype) in African-Americans (rs4821480, rs2032487, rs4821481, and rs3752462), only one SNP had a minor allele frequency (MAF) >5% in HapMap Asian samples (rs3752462, MAF = 0.43) and was genotyped in the SHFS (see also supplemental material). We then selected seven SNPs located within the haplotype E region for haplotype analyses (chromosome 22, position 35,019,747–35,034,683 bp). Haplotypes were inferred using Phase (version 2.1), which implements a Bayesian statistical method for reconstructing haplotypes from population genotype data (Stephens et al. 2001).

### Statistical analysis

Quantitative traits with non-normal distribution were log-transformed for analysis. We tested the association of SNPs (and haplotypes) of the *MYH9* gene with kidney traits using measured genotyped within the variance component models (Boerwinkle et al. 1986). Models were adjusted for the random effects of relatedness among individuals and fixed effects of age, sex, center and degree of Indian blood (as an estimate of ancestry). We also tested for population stratification using the quantitative transmission disequilibrium test in SOLAR (Havill et al. 2005). We used additive genetic models, but we also performed analyses using recessive models as these models were used in published studies in African-Americans (Kao et al. 2008; Kopp et al. 2008). In additional analysis, we excluded individuals with diabetes since the association has been described for non-diabetic CKD ($N = 59$ CKD). All analyses were performed in SOLAR using variance component models. For haplotype analyses, we used the number of copies of the haplotype. Unadjusted *P* values were reported. We used Bonferoni methods to correct for multiple testing and considered an alpha of 0.0025 (0.05/20 SNPs) for significant findings. Three individuals with a kidney transplant were removed from the analysis of GFR and albuminuria but contributed data for the CKD analyses.

## Results

Of the 1,119 genotyped individuals, 64% were women, 48% had hypertension, 37% had type 2 diabetes, and an additional 9% had impaired fasting glucose (Table 1). The mean eGFR was 90.3 ml/min/1.73 $m^2$, and the median urinary albumin to creatinine ratio was 10.7 mg/g. Twelve percent of individuals ($n = 139$) had CKD, and 32% ($n = 353$) had reduced kidney function and/or increased albuminuria. One of 1,119 individuals was excluded due to low genotyping (missing rate >0.05). All SNPs were in Hardy–Weinberg equilibrium except for rs2239784 (Table 2).

Figure 1 shows the linkage disequilibrium (LD) of the 20 genotyped SNPs that passed quality control. SNPs previously shown to be associated with kidney outcomes in African-Americans

are shown in bold in Tables 2 and 3. Using additive or recessive genetic models, we did not find significant associations among the *MYH9* SNPs and kidney traits in age-, sex- and center-adjusted models and in models adjusted for population stratification using percentage of Indian blood (Tables 2, 3; test for stratification was also not significant). In addition, the eGFR and ACR findings were not significant in analysis excluding individuals with type 2 diabetes (data not shown).

Three common haplotypes were identified within the selected gene region (Fig. 2). Inferred haplotypes were also not associated with kidney outcomes (Fig. 2).

## Discussion

The *MYH9* gene has been recently identified for genetic susceptibility of CKD in African-American individuals with ESRD, FSGS, and albuminuria (Freedman et al. 2009a, b; Kao et al. 2008; Kopp et al. 2008). Our study of American Indians was unable to replicate the association of this gene with CKD defined by either reduced kidney function or albuminuria. American Indians have a high prevalence of type 2 diabetes, obesity, and smoking, all risk factors for CKD. Although the prevalence of diabetes is high among American Indians, a large number of non-diabetic individuals have increased albuminuria (Robbins et al. 1996), suggesting that the causal mechanisms for kidney disease may be independent of diabetes. Albuminuria is highly associated with Indian blood quantum in this population (Robbins et al. 1996) suggesting a strong genetic susceptibility to CKD.

Although the rates of diabetic ESRD among American Indians have recently declined (27.7% since 1995), ESRD among diabetic individuals still accounts for most of the cases in the US in 2006 (329 per million population for a total incidence of 489 per million) (2006). *MYH9* genetic susceptibility has been described mostly for non-diabetic CKD. Therefore, it is possible that this gene is not an important genetic risk factor for CKD in American Indian populations if most of the CKD cases are due to diabetes. However, a recent study of African-Americans has shown significant association of *MYH9* with diabetic ESRD (Freedman et al. 2009a) suggesting a broad genetic risk effect across kidney diseases. Alternatively, it is possible that individuals with diabetes and ESRD may have underlying kidney disease unrelated to diabetes (Mazzucco et al. 2002). In our population of American Indians, kidney biopsy is not available, and, therefore, we cannot exclude the possibility that other causes of kidney disease are present in individuals with type 2 diabetes.

The lack of replication of these gene polymorphisms in American Indians is intriguing, and may be due to differences in LD structure in this population as compared to African-Americans and Caucasians. Although we were unable to reconstruct the at risk haplotype (E) for CKD, four of the genotyped SNPs in our study have been previously shown to be independently associated with CKD in African-Americans (SNPs in bold in Tables 2, 3). In addition, haplotype analyses using seven SNPs located within the haplotype E region were not significantly associated with kidney outcomes (Fig. 2). Given the effect size of these associations in prior published studies and the MAF for some of the SNPs (varying from 0.05 to 0.49), it is unlikely that our findings are due to low power (see supplemental material for power analyses). It is possible that the contribution of the gene for CKD risk is obscured by differences in environmental exposures in this population and gene–environment interactions. An alternative explanation is that haplotypes conferring risk in African-Americans and haplotypes conferring a protective effect in individuals of European ancestry are less common in American Indians. Identification of the actual functional genetic variation responsible for the associations seen in African-Americans will likely help to clarify the lack of replication of this gene in American Indians.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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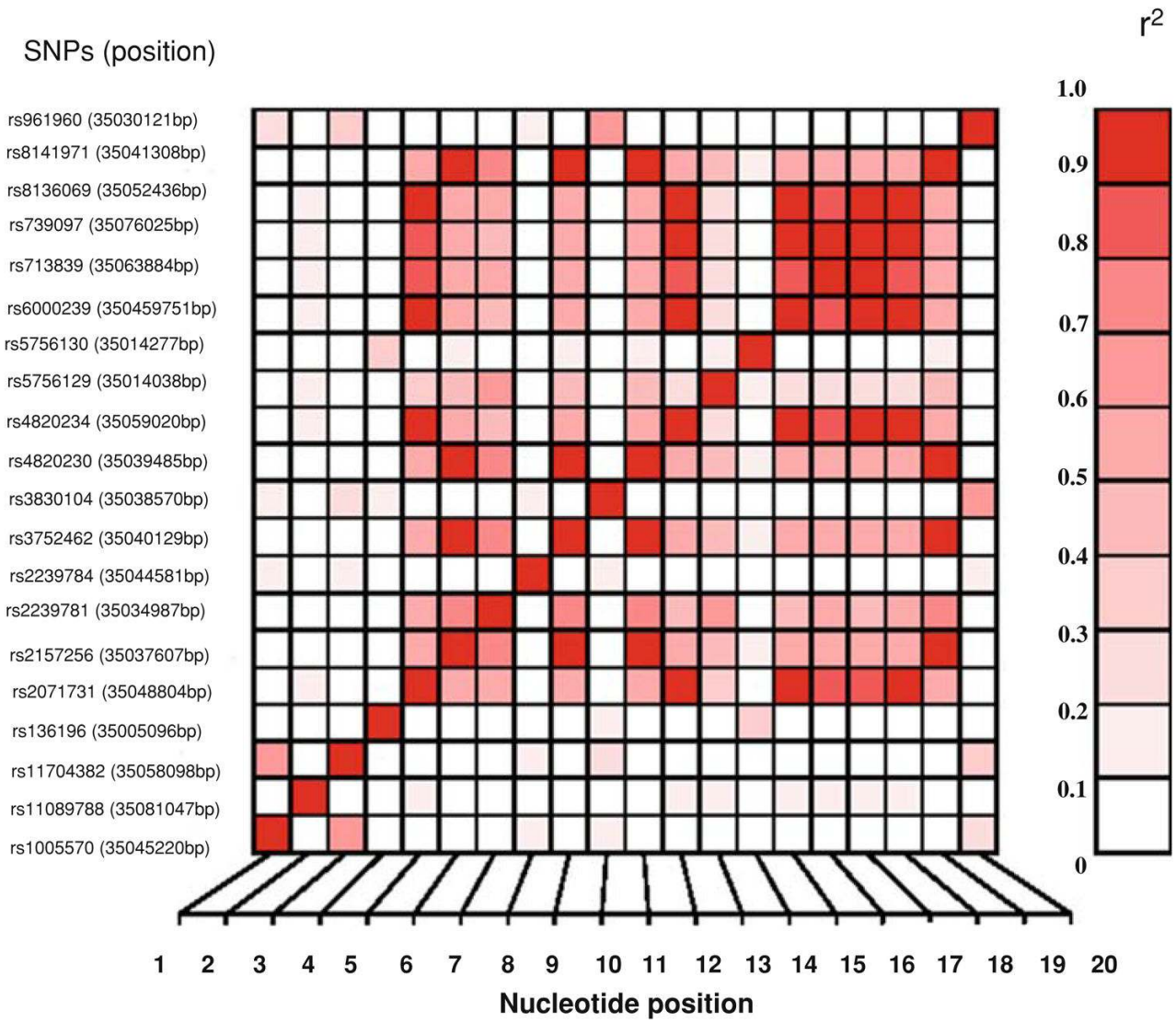


**Fig. 1.**

Linkage disequilibrium of genotyped SNPs of the MYH9 gene. SNPs are displayed in the *left column* ordered by position in base-pair. *Right column* shows the correlation among SNPs based on $r^2$

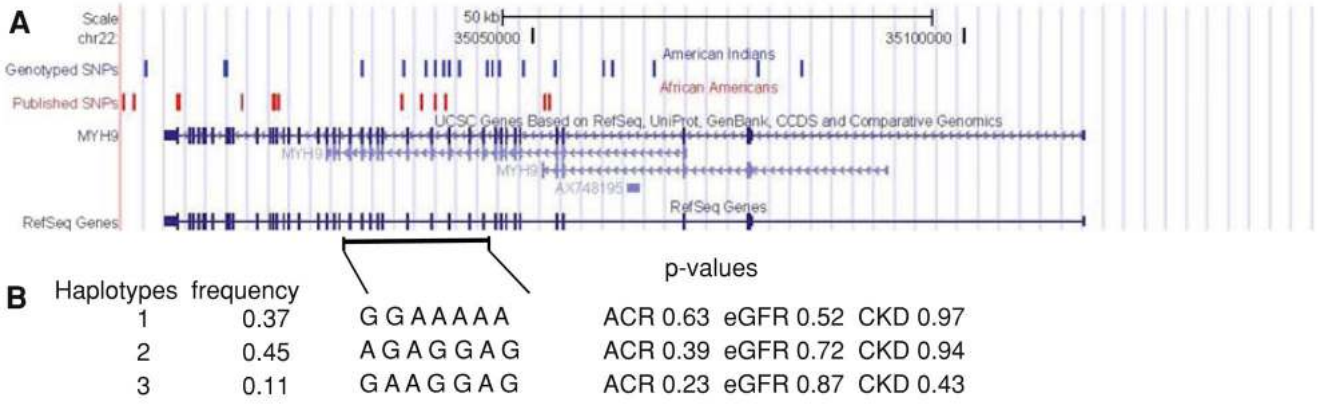


**Fig. 2.**

Location of the SNPs genotyped within the *MYH9* gene and flanking regions using NCBI Build 36.1(**a**). The figure also shows previously published SNPs genotyped in African-Americans (*Published SNPs*). Position of SNPs used to infer haplotypes (Phase v2.1) in the chromosome 22 region between 35019747 and 350334683 bp (**b**). The three most common haplotypes are displayed (SNP order: rs5756129, rs5756130, rs9619601, rs2239781, rs2157256, rs3830104, and rs3752462). *P* values for association of haplotype copies and kidney outcomes are also displayed. *ACR* albumin to creatinine ratio; *eGFR* estimated glomerular filtration rate; *CKD* chronic kidney disease

## Table 1

Characteristics of American Indians genotyped for *MYH9* SNPs on chromosome 22

| **Characteristics of the sample (*N* = 1,119)** | |
|---|---|
| Age (years), mean (SD) | 53.2 (14.7) |
| Female sex, *N* (%) | 716 (64) |
| SBP, mean (SD) | 127.7 (18.2) |
| DBP, mean (SD) | 76.5 (11.0) |
| Hypertension, *N* (%) | 542 (48) |
| Hypertension treatment, *N* (%) | 415 (37) |
| Type 2 diabetes, *N* (%) | 409 (36.6) |
| IFG, *N* (%) | 99 (8.9) |
| Current smoking, *N* (%) | 338 (30) |
| eGFR, mean (SD) | 90.3 (29.3) |
| UACR, median (interquartiles) | 10.7 (6.1, 31.3) |
| CKD, *N* (%) | 139 (12) |
| Microalbuminuria, *N* (%) | 201 (18.2) |
| Macroalbuminuria, *N* (%) | 82 (7.4) |

*SD* standard deviation; *N* number; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *IFG* impaired fasting glucose; *UACR* urine albumin to creatinine ratio; *eGFR* estimated glomerular filtration rate; *CKD* chronic kidney disease, defined by a eGFR <60 or dialysis or kidney transplantation

**Table 2**

The association of SNPs in the *MYH9* gene and kidney function in American Indians of the Strong Heart Family Study

| SNPs | Position Build 36.1 | Location | Alleles | Reference allele | MAF | HWE | eGFR beta (SE)* | *P* value | CKD OR (95% CI)* | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| rs136196 | 35,005,096 | 3′ region | A/G | A | 0.23 | 0.87 | 1.16 (1.17) | 0.33 | 0.98 (0.70, 1.35) | 0.89 |
| **rs5756129** | 35,014,038 | intron 34 | G/A | A | 0.49 | 0.90 | 0.93 (1.00) | 0.35 | 1.05 (0.80, 1.38) | 0.72 |
| **rs5756130** | 35,014,277 | exon 34 (syn codon 1,633) | A/G | G | 0.11 | 0.65 | −0.62 (1.58) | 0.70 | 1.10 (0.70, 1.70) | 0.69 |
| rs9619601 | 35,030,121 | exon 19 (syn codon) | G/A | A | 0.03 | 0.63 | −3.57 (2.81) | 0.20 | 1.07 (0.47, 2.41) | 0.88 |
| rs2239781 | 35,034,987 | intron 15 | A/G | A | 0.37 | 0.20 | −1.01 (1.02) | 0.32 | 1.02 (0.78, 1.35) | 0.87 |
| rs2157256 | 35,037,607 | intron 14 | A/G | A | 0.43 | 0.22 | −0.85 (0.99) | 0.39 | 1.04 (0.79, 1.36) | 0.79 |
| rs3830104 | 35,038,570 | intron 13 | G/A | A | 0.04 | 0.16 | −1.54 (2.49) | 0.54 | 0.86 (0.44, 1.71) | 0.67 |
| rs4820230 | 35,039,485 | intron 13 | G/A | G | 0.43 | 0.22 | −0.85 (0.99) | 0.39 | 1.04 (0.79, 1.36) | 0.79 |
| **rs3752462** | 35,040,129 | intron 13 | A/G | A | 0.43 | 0.22 | −0.85 (0.99) | 0.39 | 1.04 (0.79, 1.36) | 0.79 |
| rs8141971 | 35,041,308 | intron 12 | A/G | A | 0.43 | 0.25 | −0.84 (0.99) | 0.40 | 1.04 (0.79, 1.37) | 0.78 |
| rs2239784 | 35,044,581 | intron 10 | A/G | A | 0.04 | 0.005 | 1.92 (2.30) | 0.41 | 1.02 (0.56, 1.86) | 0.96 |
| **rs1005570** | 35,045,220 | intron 10 | A/G | A | 0.05 | 0.50 | 2.16 (2.38) | 0.36 | 1.09 (0.54, 2.21) | 0.80 |
| rs6000239 | 35,045,975 | intron 9 | A/G | A | 0.44 | 0.05 | −0.1245 (0.98) | 0.90 | 1.04 (0.79, 1.36) | 0.79 |
| rs2071731 | 35,048,804 | intron 5 | A/G | A | 0.42 | 0.22 | −0.15 (0.98) | 0.88 | 1.03 (0.79, 1.36) | 0.81 |
| rs8136069 | 35,052,436 | intron 5 | A/C | A | 0.43 | 0.20 | −0.18 (0.99) | 0.86 | 1.03 (0.78, 1.35) | 0.83 |
| rs11704382 | 35,058,098 | intron 1 | A/C | C | 0.04 | 0.64 | −5.06 (2.68) | 0.06 | 0.97 (0.43, 2.18) | 0.94 |
| rs4820234 | 35,059,020 | intron 3 | A/G | A | 0.44 | 0.30 | −0.20 (0.99) | 0.86 | 1.03 (0.79, 1.35) | 0.83 |
| rs713839 | 35,063,884 | intron 3 | A/G | A | 0.44 | 0.63 | −0.09 (1.00) | 0.95 | 1.05 (0.80, 1.39) | 0.71 |
| rs739097 | 35,076,025 | intron 1 | G/A | G | 0.45 | 0.33 | 0.02 (0.99) | 0.99 | 1.00 (0.76, 1.31) | 1.00 |
| rs11089788 | 35,081,047 | intron 1 | A/C | A | 0.35 | 0.15 | −0.03 (1.06) | 0.97 | 0.98 (0.73, 1.31) | 0.90 |

Position based on Build 36, dbSNP version 128

SNPs genotyped in prior studies are in bold

eGFR truncated at 15 and 200

*eGFR* estimated glomerular filtration rate; *CKD* chronic kidney disease; *HWE* Hardy–Weinberg equilibrium; *MAF* minor allele frequency; *SE* standard error; *OR* odds ratio; *CI* confidence interval

*Adjusted for age, age$^2$, sex and center

**Table 3**

The association of SNPs in the *MYH9* gene and urine albumin in American Indians of the Strong Heart Family Study

| SNPs | Reference allele | ACR (< 30 vs. ≥30 mg/g creatinine) OR (95% CI)* | *P* value | LACR (mg/g creatinine) beta (SE)* | *P* value |
|---|---|---|---|---|---|
| rs136196 | A | 0.95 (0.74, 1.21) | 0.65 | −0.05 (0.08) | 0.55 |
| **rs5756129** | A | 1.00 (0.94, 1.05) | 0.44 | 0.04 (0.07) | 0.57 |
| **rs5756130** | G | 1.09 (0.79, 1.51) | 0.61 | −0.02 (0.11) | 0.88 |
| rs9619601 | A | 1.01 (0.55, 1.84) | 0.98 | 0.10 (0.20) | 0.60 |
| rs2239781 | A | 1.09 (0.89, 1.33) | 0.40 | −0.03 (0.07) | 0.66 |
| rs2157256 | A | 1.04 (0.86, 1.27) | 0.68 | −0.04 (0.07) | 0.56 |
| rs3830104 | A | 1.10 (0.64, 1.89) | 0.73 | 0.07 (0.18) | 0.70 |
| rs4820230 | G | 1.04 (0.86, 1.27) | 0.68 | −0.04 (0.07) | 0.56 |
| **rs3752462** | A | 1.04 (0.86, 1.27) | 0.68 | −0.04 (0.56) | 0.56 |
| rs8141971 | A | 1.05 (0.86, 1.27) | 0.65 | −0.04 (0.07) | 0.53 |
| rs2239784 | A | 1.36 (0.87, 2.14) | 0.18 | −0.33 (0.16) | 0.04 |
| **rs1005570** | A | 1.21 (0.73, 2.00) | 0.46 | −0.23 (0.17) | 0.17 |
| rs6000239 | A | 0.97 (0.80, 1.18) | 0.79 | 0.03 (0.07) | 0.61 |
| rs2071731 | A | 1.00 (0.82, 1.21) | 0.96 | 0.02 (0.07) | 0.74 |
| rs8136069 | A | 0.98 (0.80, 1.19) | 0.82 | 0.03 (0.07) | 0.70 |
| rs11704382 | C | 0.77 (0.44, 1.35) | 0.37 | 0.22 (0.19) | 0.25 |
| rs4820234 | A | 1.02 (0.83, 1.24) | 0.87 | 0.0001 (0.07) | 1.00 |
| rs713839 | A | 1.01 (0.83, 1.24) | 0.89 | −0.0003 (0.07) | 1.00 |
| rs739097 | G | 1.02 (0.84, 1.24) | 0.85 | −0.003 (0.07) | 0.96 |
| rs11089788 | A | 0.92 (0.74, 1.14) | 0.44 | −0.04 (0.07) | 0.60 |

SNPs genotyped in prior studies are in bold

*$N$ = 1,054–1,058, adjusted for age, age$^2$, sex, center and percentage of Indian blood

*ACR* urine albumin to creatinine ratio categories (<30 vs. ≥30 mg/g creatinine); *LACR* log-transformed continuous urine albumin to creatinine ratio; *SE* standard error; *OR* odds ratio; *CI* confidence interval