

Supplementary Note

Clinical data for study subjects

Patients with biopsy-proven FSGS were referred from nephrologists at 24 centers within the United States or by self-referral to the NIDDK, NIH. In all cases the renal biopsies were performed based upon clinical indications, not as a part of the present study. Inclusion and exclusion criteria, by group are the following:

1) Patients with FSGS: renal biopsy showing focal and segmental glomerulosclerosis (FSGS). Included were adult and pediatric patients with idiopathic FSGS and HIV-1-associated FSGS with pathological features of FSGS and collapsing FSGS, respectively. Patients with hyperfiltration FSGS (reduced renal mass, chronic interstitial nephritis, sickle cell anemia, or obesity with BMI.40 kg/m²) were excluded. Renal function and date of initiation of renal replacement therapy was recorded patients at baseline and follow-up visits.

2) Hypernormal controls with HIV-1 infection and without kidney disease: Adults with serologically confirmed HIV-1 infection for ≥ 8 years and lacking clinical renal disease, as evidenced by normal serum creatinine concentrations and urine protein/creatinine ratio <0.5 g/g or 24 hour urine protein excretion < 500 mg/day. Participants were enrolled in the AIDS Link to the Intravenous Experience Cohort Study (ALIVE) in Baltimore, Maryland.

3) Normal blood donors were from the NIH Blood Bank and the National Cancer Institute-Frederick normal donor programs. Participants were excluded if they belonged to an HIV-1 risk group or tested seropositive for HIV-1 infection or had evidence or history of renal disease.

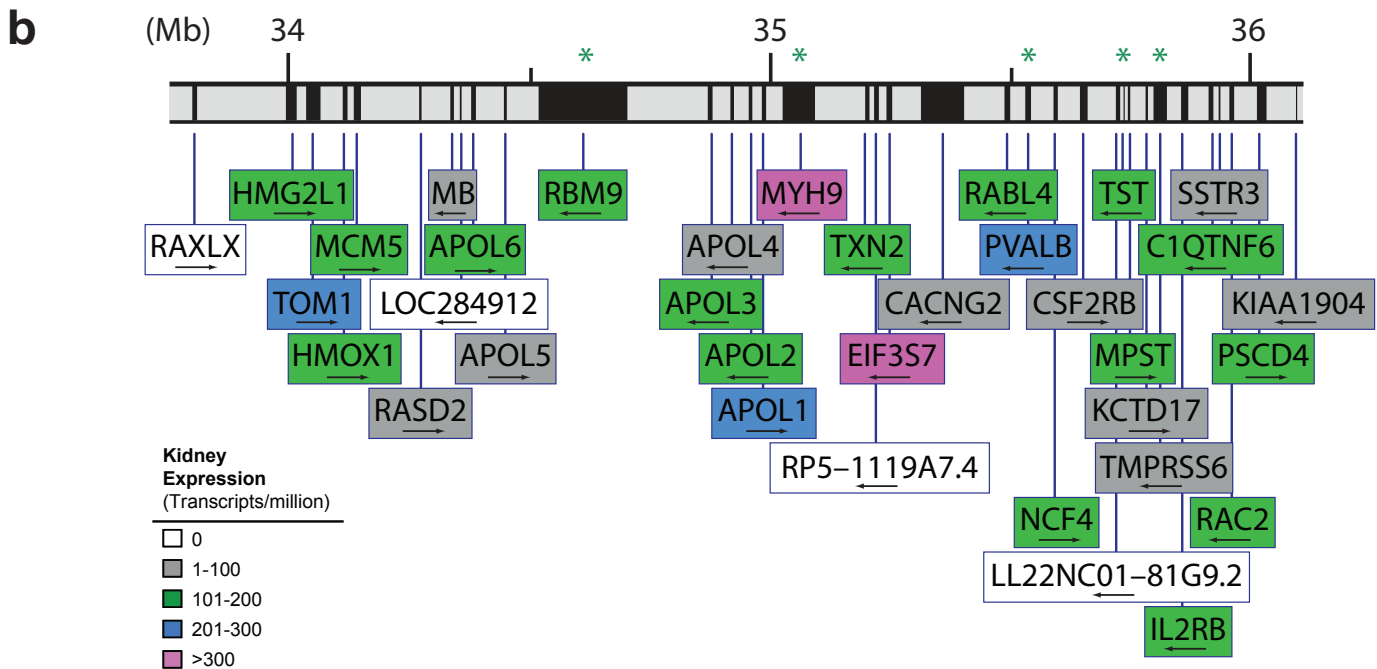
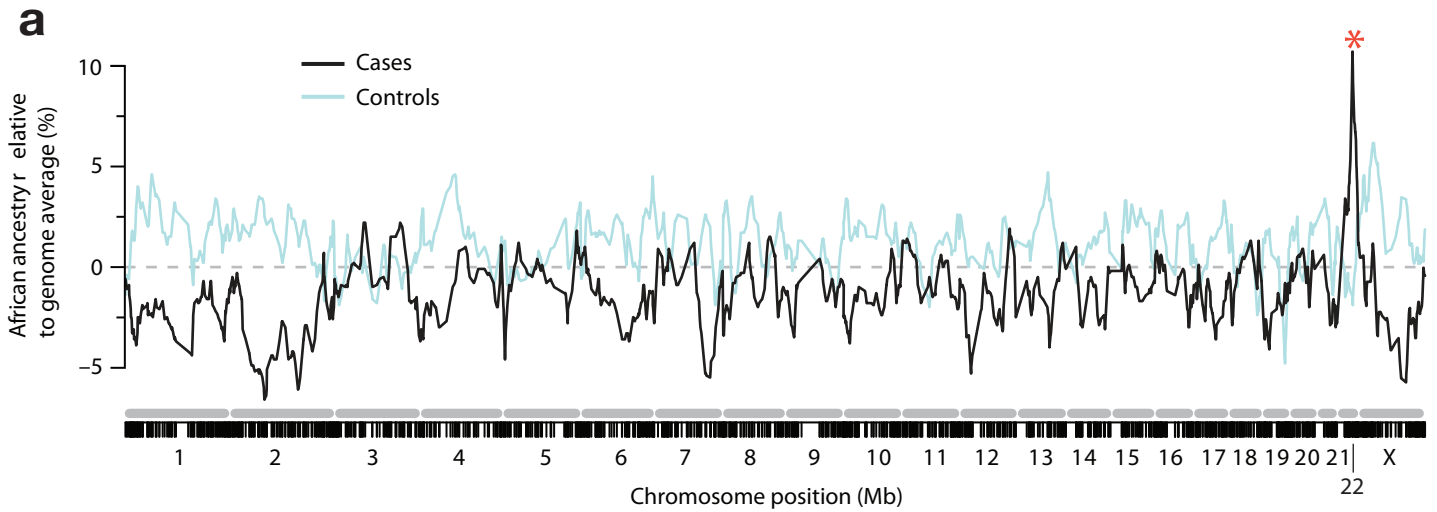
Wake Forest University School of Medicine (WFUSM) Extension Cohorts

WFUSM cases and controls were recruited at dialysis facilities, medical clinics, or community health screenings. All individuals were born in North Carolina, South Carolina, Virginia, Georgia or Tennessee.

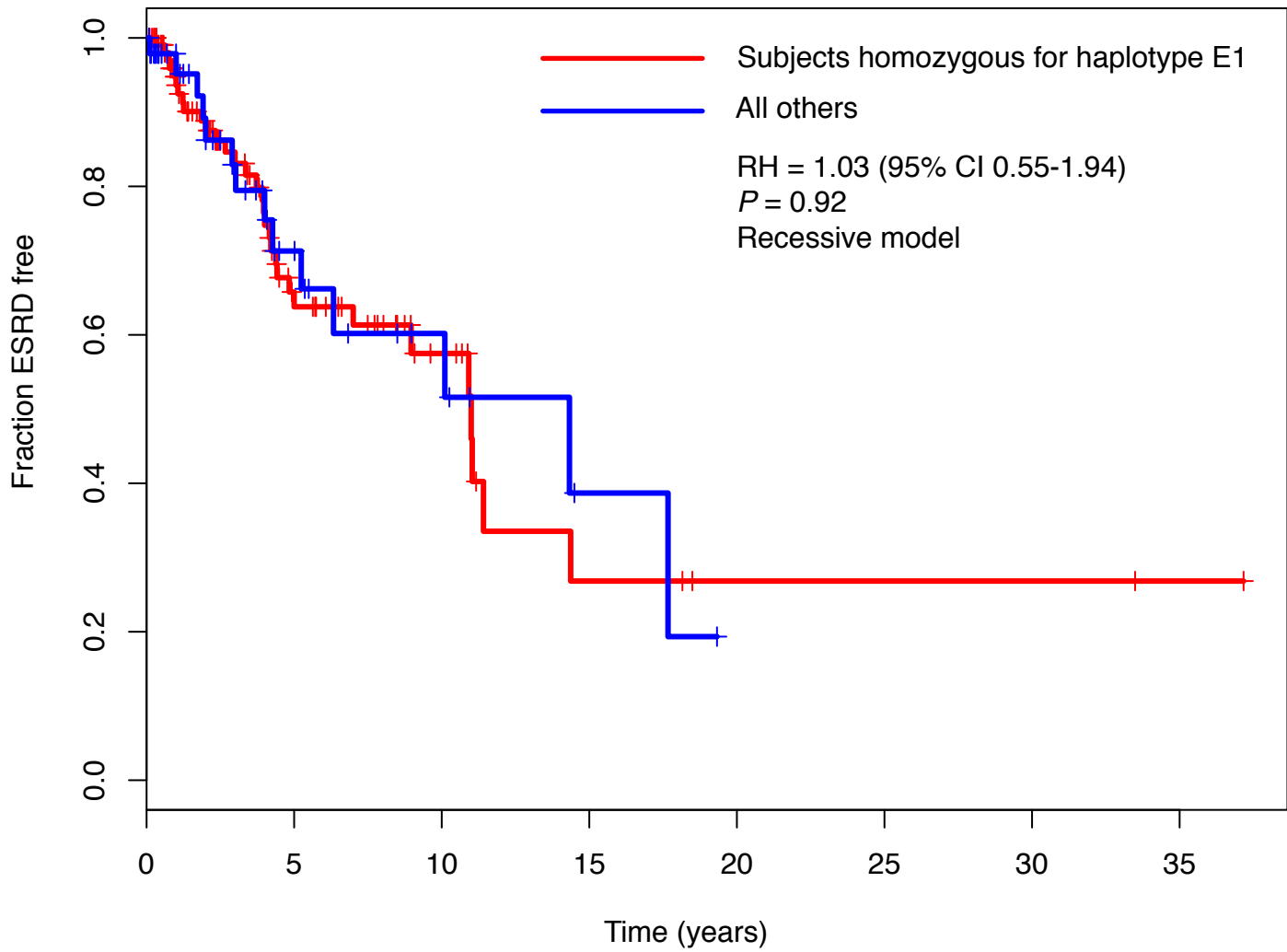
1) Hypertension-associated ESRD (H-ESRD) was diagnosed when high blood pressure preceded initiation of renal replacement therapy in the presence of hypertensive target organ damage and either low level proteinuria (≤ 30 mg/dL on urine dipstick, <0.5 gram protein/24 hours on timed urine collection, or urine protein:creatinine ratio <0.5 g/g) or in the absence of quantification of proteinuria.

2) Type 2 diabetes-associated ESRD was diagnosed when diabetes developed after the age of 34 years with ≥ 5 years diabetes duration prior to dialysis onset in the presence of either diabetic retinopathy and/or proteinuria exceeding 500 mg/day or 100 mg/dl on urinalysis.

3) Unrelated, non-diabetic control subjects - denied a personal or family history (first degree relatives) of diabetes or kidney disease, kidney failure, dialysis or kidney transplantation.



Supplementary Figure 1 (a) The change in African ancestry across the genome. A comparison to the genome average for cases (black) and controls (teal) from the ANCESTRY-MAP analysis is shown. The elevated African ancestry of cases on chromosome 22 is marked with a red asterisk (*). The X axis consists of a concatenated set of chromosomes (gray) with MALD markers interrogated indicated below (black). (b) 35 genes within the 95% credible interval of the MALD chromosome 22 peak. The chromosomal segment (coordinates for build 36) is shown with genes in black; MYH9 and the four genes with SNPs typed for negative controls in the fine mapping analysis are noted by asterisks. Genes are colored according to reported levels of expression in kidney in transcripts/million: white 0; gray 1-100; green 101-200; blue 201-300; red >300. Data from Gene Expression Omnibus (<http://www.ncbi.nlm.nih.gov/geo/>) and reference 24.



Supplementary Figure 2 Kaplan-Meier plot of progression to ESKD for 161 African American FSGS cases, comparing subjects homozygous for the FSGS susceptibility haplotype E-1 with all other subjects. Cox model results for this comparison are shown.

Supplementary Table 1 *MYH9* and adjacent gene SNP associations with FSGS for African Americans, and limited to subjects with only local African ancestry at the tested SNP

		African-American FSGS cases (n=190) and controls (n=222) with MALD data					2x local African Ancestry (n=245) ^a		
Gene	SNP	Genomic position	Association at SNP ^b		Admixture Association not explained by SNP		Percentage of locus-specific FSGS association explained by SNP genotype alone	OR	P
			X ²	P ^c	X ²	P			
<i>RBM9</i>	rs5750175	34.479	0.7	0.39	57.0	4x10⁻¹⁴	1	1.37	0.14
	rs5755943	34.496	0.7	0.41	49.5	2x10⁻¹²	1	0.98	1
	rs7078	35.008	11.0	0.0009	40.6	2x10⁻¹⁰	21	3.07	0.005
	rs12107	35.008	11.1	0.0009	42.2	8x10⁻¹¹	21	3.08	0.03
	rs735853	35.009	37.8	8x10⁻¹⁰	22.7	2x10⁻⁶	62	∞ ^d	0.10
	rs5756129	35.014	21.6	3x10⁻⁶	42.6	7x10⁻¹¹	34	3.39	0.0001
	rs5756130	35.014	9.2	0.002	55.9	8x10⁻¹⁴	14	3.21	0.001
	rs11549907	35.015	5.3	0.02	52.2	5x10⁻¹³	9	1.70	0.18
	rs875725	35.022	11.5	0.0007	56.1	7x10⁻¹⁴	17	1.97	0.092
	rs2187776	35.025	1.5	0.22	46.4	1x10⁻¹¹	3	0.99	1
<i>MYH9</i>	rs4821480	35.025	61.5	4x10⁻¹⁵	12.6	0.0004	83	3.24	0.003
	rs2032487	35.025	59.8	1x10⁻¹⁴	15.5	8x10⁻⁵	79	2.80	0.0004
	rs4821481	35.026	64.4	1x10⁻¹⁵	13.0	0.0003	83	3.21	6x10⁻⁵
	rs3752462	35.040	44.5	3x10⁻¹¹	24.5	8x10⁻⁷	65	3.17	1x10⁻⁴
	rs5756152	35.042	48.0	4x10⁻¹²	33.1	9x10⁻⁹	59	2.26	5x10⁻⁵
	rs1557539	35.044	5.7	0.02	52.3	5x10⁻¹³	10	3.59	0.34
	rs1005570	35.045	48.2	4x10⁻¹²	29.5	6x10⁻⁸	62	2.30	5x10⁻⁵
	rs16996674	35.057	25.9	4x10⁻⁷	38.4	6x10⁻¹⁰	40	1.48	0.05
	rs16996677	35.057	32.0	2x10⁻⁸	35.8	2x10⁻⁹	47	1.59	0.02
	rs736721	35.533	11.1	0.0009	38.5	5x10⁻¹⁰	22	1.28	0.26
<i>PVALB</i>	rs739031	35.538	11.6	0.0007	39.3	4x10⁻¹⁰	23	1.32	0.20
	rs2269511	35.541	0.7	0.41	41.4	1x10⁻¹⁰	2	0.95	0.85
	rs5756477	35.737	1.3	0.25	36.0	2x10⁻⁹	4	1.06	0.85
<i>TST</i>	rs130598	35.738	2.4	0.12	33.5	7x10⁻⁹	7	1.08	0.80
	rs470029	35.740	6.7	0.01	30.1	4x10⁻⁸	18	1.24	0.36
	rs855788	35.804	22.4	2x10⁻⁶	17.2	3x10⁻⁵	57	2.27	0.085
	rs855787	35.805	2.7	0.10	32.4	1x10⁻⁸	8	0.99	1
<i>TMPRSS6</i>	rs2543519	35.810	4.8	0.03	31.0	3x10⁻⁸	13	1.34	0.13
	rs1421312	35.818	0.7	0.41	34.3	5x10⁻⁹	2	0.88	0.55

^aLimited to individuals predicted with greater than 95% confidence to carry two African derived chromosomal segments at the locus.

^bX², Odds ratio (OR) and P are for logistic regression for the additive genetic model.

^cAssociations that are significant after correction (under the Bonferroni cutoff of P < 0.0005; see methods) are shown in bold.

^d∞: Infinite, OR has zero in denominator since factor is absent from controls or is always present in cases.

Supplementary Table 2 *MYH9* SNP and haplotype associations with FSGS^a for all African Americans cases and controls

Variant	Alleles		Normal Control risk allele freq. (%) ^b		Risk allele			
			European American	African American	Dominant		Recessive	
	Ref.	Risk	American	American	OR (95% CI) ^c	P ^d	OR (95% CI)	P
rs7078	G	A	72.9	85.2	1.82 (0.5,9.99)0	0.42	2.5 (1.63, 3.93)	8X10⁻⁶
rs12107	A	G	85.3	89.1	∞ (0.45, ∞) ^e	0.19	3.17 (1.84,5.76)	4X10⁻⁶
rs735853	G	C	51.9	88.3	4.33 (0.62,187.3)	0.20	8.82 (4.07,22.72)	5X10⁻¹³
rs5756129	C	T	77.9	79.3	13.21 (2.18,539)	0.0003	2.78 (1.88,4.19)	4X10⁻⁸
rs5756130	T	C	97.6	87.5	∞ (0.87, ∞)	0.07	2.11 (1.35,3.37)	0.0005
rs11549907	A	G	98.5	93.7	1.14 (0.09,60.23)	1	1.61 (0.96,2.81)	0.08
rs875725	C	T	98.5	92.8	0.77 (0.04,45.74)	1	1.91 (1.15,3.27)	0.009
rs2187776	T	C	3.1	30.1	1.31 (0.96,1.8)	0.08	1.26 (0.75,2.1)	0.37
rs4821480	T	G	4.3	67.4	4.81 (2.18,12.56)	5X10⁻⁶	4.77 (3.27,7.07)	2X10⁻¹⁹
rs2032487	T	C	4.3	63.7	5.01 (13.06,2.27)	2X10⁻⁶	4.21 (2.97,6.01)	2X10⁻¹⁸
rs4821481	T	C	4.3	62.3	5.04 (2.29, 13.15)	2X10⁻⁶	4.54 (3.21,6.48)	1X10⁻²⁰
rs3752462	C	T	31.0	72.0	5.30 (1.66,27.07)	0.001	3.86 (2.67,5.66)	4X10⁻¹⁵
rs5756152	G	A	2.6	26.1	3.37 (2.39,4.80)	1X10⁻¹³	4.91 (3.12,7.80)	3X10⁻¹³
rs1557539	C	G	99.6	97.5	∞ (0.07, ∞)	1	2.04 (0.88,5.51)	0.11
rs1005570	G	A	7.9	41.8	4.40 (2.74,7.33)	2X10⁻¹²	3.80 (2.70,5.37)	3X10⁻¹⁵
rs16996674	C	T	<1	23.5	2.62 (1.89,3.65)	1X10⁻⁹	4.06 (2.48,6.69)	7X10⁻⁹
rs16996677	G	A	<1	26.2	2.80 (2.01,3.92)	1X10⁻¹⁰	3.89 (2.50,6.09)	4X10⁻¹⁰
Haplotypes								
E-1	GCCT		4.1	59.7	4.68 (2.32,11.38)	2X10⁻⁶	4.98 (3.54,7.07)	4X10⁻²³
E-2	TTTC		69.0	20.5	0.21 (0.13,0.34)	1X10⁻¹³	0.15 (0.02,0.61)	0.002
E-3	TTTT		26.9	11.9	0.43 (0.26,0.68)	0.0002	0.00 (0.00,0.61)	0.003
E-4	GTTC		<1	4.0	0.76 (0.38,1.45)	0.46	-	-
E-5	GCCC		<1	3.2	0.48 (0.19,1.06)	0.07	-	-

^aAssociation analysis for combined idiopathic or HIV-associated FSGS (241 cases and 611 controls).

^bPopulation frequencies for normal controls in European Americans (n=221) and African Americans (n=370). ^cOdds ratio confidence intervals and probabilities calculated with a Fisher's exact test. ^dTests that are significant after correction (under the Bonferroni cutoff of P < 0.0005; see methods) are shown in bold. ^eOdds Ratios with a denominator equal to zero are shown as infinite (∞).

Supplementary Table 3 *MYH9* associations in idiopathic FSGS, HIV-1 associated FSGS, and hypertensive ESKD, dominant model for risk factor

Variant	African Americans				European-Americans			
	Idiopathic FSGS(n=587) ^a		HIV-associated FSGS (n=298)		Hypertensive End Stage Kidney Disease (n=433) ^b		Idiopathic FSGS (n=411)	
	OR	<i>P</i> _{FET} ^c	OR	<i>P</i> _{FET}	OR	<i>P</i> _{FET}	OR	<i>P</i> _{FET}
rs7078	1 (0.21,6.27)	1	∞,(0.37,∞) ^e	0.36	NT ^d	NT	0.88 (0.39,2.05)	0.85
rs12107	∞,(0.09,∞)	1	∞,(0.14,∞)	1	0 (0,48)	1.00	0.53 (0.07,3.99)	0.42
rs735853	3.55 (0.45,161.13)	0.28	∞,(0.14,∞)	1	2.49 (0.35,27.81)	0.41	0.85 (0.48,1.51)	0.58
rs5756129	11.88 (1.89,493.19)	0.001	∞,(0.48,∞)	0.22	1.62 (0.52,5.22)	0.44	1.03 (0.35,3.44)	1
rs5756130	0.53 (0.31,0.88)	0.10	0.28 (0.07,0.82)	1	2.46 (0.35,27.48)	0.42	— ^f	—
rs11549907	0.88 (0.47,1.59)	1	0.2 (0.02,0.82)	1	NT	NT	0 (0,20.91)	0.35
rs875725	0.72 (0.39,1.29)	1	0.24 (0.05,0.8)	—	0 (0,48.04)	1	—	—
rs2187776	1.3 (0.9,1.89)	0.17	1.43 (0.75,2.77)	0.29	1.09 (0.73,1.62)	0.70	1.77 (0.7,4.48)	0.19
rs4821480	4.12 (1.81,10.99)	0.0001	∞,(1.55,∞)	0.006	1.81 (0.92,3.66)	0.08	1.55 (0.7,3.36)	0.26
rs2032487	4.3 (1.89,11.46)	7x10⁻⁵	∞,(1.57,∞)	0.006	NT	NT	1.55 (0.7,3.36)	0.26
rs4821481	4.32 (1.9,11.5)	7x10⁻⁵	∞,(1.63,∞)	0.007	1.36 (0.73,2.53)	0.30	1.56 (0.71,3.37)	0.26
rs3752462	4.77 (1.44,24.89)	0.005	∞,(0.6,∞)	0.13	3.37 (1.31,9.78)	0.006	1.06 (0.67,1.68)	0.82
rs5756152	2.98 (2,4.48)	1x10⁻⁸	5.53 (2.52,13.5)	1x10⁻⁶	2.06 (1.37,3.11)	0.0003	1.73 (0.64,4.63)	0.24
rs1557539	0.71 (0.22,1.92)	1	0.23 (0.01,1.5)	1	NT	NT	—	—
rs1005570	4.5 (2.64,8.05)	4x10⁻¹⁰	4.94 (1.71,19.57)	0.0007	1.68 (1.02,2.77)	0.03	0.92 (0.47,1.76)	0.88
rs16996674	2.57 (1.75,3.8)	5x10⁻⁷	3.08 (1.55,6.39)	0.0007	1.4 (0.94,2.09)	0.10	∞,(0.35,∞)	0.12
rs16996677	2.69 (1.82,3.99)	1x10⁻⁷	3.41 (1.68,7.34)	0.0007	1.36 (0.9,2.04)	0.14	∞,(0.35,∞)	0.12
Haplotype								
E-1	3.99 (1.83,9.91)	6x10⁻⁵	∞,(1.75,∞)	0.004	2.45 (1.26,4.89)	0.005	1.63 (0.74,3.58)	0.18
E-2 ^g	0.16 (0.02,0.64)	0.003	0 (0,2.69)	0.36	0.36 (0.08,1.3)	0.09	0.95 (0.6,1.5)	0.82
E-3	0 (0,0.78)	0.02	0 (0,3.19)	0.36	1.24 (0.14,15)	1	1.67 (0.68,4.03)	0.21
E-4	—	—	—	—	—	—	—	—
E-5	—	—	—	—	—	—	—	—

^aFor idiopathic and HIV-associated FSGS in African-Americans, comparisons significant after correction are shown in bold.

^bFor ESKD and European-American FSGS, nominally significant associations confirmatory of highly significant associations (supplementary table 2) in African American FSGS are shown in bold. ^cFisher's exact test. ^dNot genotyped for SNP. ^einfinity, odds ratio with a denominator equal to zero. ^fRare genotype or haplotype absent from both cases and controls. ^gFor haplotypes E-2 to E-5 the recessive model is given (corresponding to taking absence of the haplotype as a dominant susceptible factor).

Supplementary Table 4 MYH9 Haplotype associations with FSGS and End Stage Kidney Disease (ESKD)

				African Americans								European Americans	
				Idiopathic FSGS (N = 558)		HIV-associated FSGS (N = 294)		Type 2 Diabetes-associated ESKD (N = 476)		Hypertensive-associated ESKD (N = 433)		Idiopathic FSGS (N = 346)	
Frequency				OR ^c	P _{FET}	OR	P _{FET}	OR	P _{FET}	OR	P _{FET}	OR	P _{FET}
a) Haplotypes for defined haplotype blocks ^a													
Haplotypes for SNPs rs5756130 to rs11549907													
		African American	European American ^b										
B1-1 ^d	CGT	0.82	0.95	1.61	0.01	3.24	0.002	NT ^e	NT	NT	NT	0.43	0.02
B1-2	TGT	0.10	0.03	0.54	0.01	0.36	0.06	NT	NT	NT	NT	2.71	0.02
B1-3	CAC	0.06	< 0.01	1.12	0.77	0.26	0.07	NT	NT	NT	NT	—	—
B1-4	CGC	0.01	< 0.01	0	0.03	0.51	1	NT	NT	NT	NT	—	—
Haplotypes for SNPs rs2187776 to rs4821481													
B2-1	TGCC	0.39	0.017	2.12	1x10 ⁻⁸	2.24	0.0003	0.95	0.72	1.28	0.06	1.90	0.26
B2-2	CGCC	0.31	0.034	1.21	0.17	1.38	0.19	1.22	0.17	1.19	0.23	1.92	0.14
B2-3	TTTT	0.25	0.895	0.27	6x10 ⁻¹⁵	0.18	9x10 ⁻⁸	0.97	0.88	0.73	0.02	0.51	0.04
B2-4	TCTT	0.04	< 0.01	0.95	1	0.26	0.22	0.52	0.05	0.48	0.02	—	—
Haplotypes for SNPs rs3752462 to rs5756152													
B4-1	TG	0.45	0.305	0.79	0.07	0.80	0.38	0.89	0.42	0.83	0.15	1.18	0.35
B4-2	TA	0.32	0.028	2.67	4x10 ⁻¹³	2.99	1x10 ⁻⁶	1.28	0.11	1.72	0.0001	1.72	0.25
B4-3	CG	0.23	0.667	0.33	7x10 ⁻¹¹	0.17	6x10 ⁻⁷	0.90	0.49	0.69	0.01	0.80	0.18
Haplotypes for SNPs rs16996674 to rs16996677													
B7-1	CG	0.68	1	0.41	3x10 ⁻¹¹	0.39	2x10 ⁻⁵	1.12	0.46	0.79	0.08	0.00	0.12
B7-2	TA	0.29	< 0.01	2.41	2x10 ⁻¹⁰	2.40	0.0001	0.84	0.28	1.22	0.17	—	—
B7-3	CA	0.03	< 0.01	1.51	0.27	2.35	0.24	1.44	0.54	1.53	0.35	—	—
b) Maximal length robustly inferred haplotypes ^f													
Haplotypes for SNPs rs735853 to rs4821481													
M1-1	CTCTTGCC	0.32	< 0.01	3.07	8E-07	2.36	3E-10	1.07	0.70	1.49	0.005	—	—
M1-2	CTCTCGCC	0.30	0.03	1.34	0.23	1.20	0.18	1.24	0.15	1.17	0.25	1.98	0.09
M1-3	CTCTTTTT	0.07	0.24	0.52	0.28	0.64	0.12	0.78	0.36	0.76	0.26	0.66	0.03
M1-4	GTCCTTTTT	0.07	0.42	0.21	0.01	0.16	2E-07	0.72	0.21	0.74	0.20	0.96	0.81
M1-5	CTCCTGCC	0.06	< 0.01	0.33	0.06	0.88	0.68	0.72	0.30	0.71	0.26	—	—
M1-6	CCCTTTTT	0.06	0.18	0.00	0.002	0.28	0.0002	0.82	0.50	0.70	0.18	1.07	0.77
M1-7	CCTTTTTT	0.05	0.03	0.26	0.06	0.26	0.0002	1.47	0.19	0.87	0.67	2.60	0.03
M1-8	CCTTTGTT	0.04	< 0.01	0.25	0.22	0.97	1	0.55	0.09	0.47	0.02	—	—
Haplotypes for SNPs rs3752462 to rs1557539													
M2-1	TGG	0.45	0.31	0.82	0.38	0.78	0.07	0.94	0.64	0.86	0.23	1.17	0.39
M2-2	TAG	0.30	0.02	3.66	2E-08	2.80	5E-14	1.21	0.24	1.73	0.0002	1.50	0.45
M2-3	CGG	0.22	0.65	0.15	3E-07	0.31	8E-11	0.87	0.40	0.67	0.008	0.79	0.16
M2-4	TAC	0.02	< 0.01	0	0.05	0.73	0.78	1.39	0.63	1.03	1	—	—
Haplotypes for SNPs rs1557539 to rs16996677													
M3-1	GGCG	0.48	0.91	0.32	1E-06	0.37	5E-14	1.24	0.11	0.83	0.15	1.18	0.66
M3-2	GATA	0.29	< 0.01	2.49	7E-05	2.39	3E-10	0.85	0.31	1.26	0.10	—	—
M3-3	GACG	0.18	0.07	1.54	0.12	1.40	0.05	0.74	0.10	0.91	0.57	0.71	0.36
M3-4	GACA	0.03	< 0.01	2.31	0.24	1.48	0.27	1.28	0.67	1.48	0.45	—	—
M3-5	CGCG	0.02	< 0.01	0	0.22	0.45	0.29	1.92	0.24	1.41	0.63	—	—

^aHaplotype blocks as defined by the confidence interval method (reference 38), using the standard parameter setting. In general the block haplotypes are not fully resolved as only a subset of the tagging SNPs were typed.

^bAnalysis was not done for haplotypes with frequency < 1%. There were no haplotypes unique to European-Americans with frequency \geq 1%.

^cOR and P_{FET} (FET: Fisher exact test) are for an allele model.

^dHaplotypes are numbered by haplotype block within MYH9 coding region and in order of decreasing frequency within blocks.

^eNT: SNPs needed to infer these haplotypes not typed in this group.

^fLongest haplotypes that could be inferred with uncertainty < 2% (uncertainty measured as entropy; < 2% of maximal entropy)

Supplementary Table 5 Association of MYH9 SNPs and haplotypes with Type II Diabetes End Stage Kidney Disease (n=476)

Variant	Risk Allele Dominant		Risk Allele Recessive	
	OR	P_{FET}	OR	P_{FET}
rs7078	NT ^a	NT	NT	NT
rs12107	0.00	0.52	1.24	0.45
rs735853	2.98	0.23	1.04	0.91
rs5756129	1.11	0.82	0.85	0.44
rs5756130	0.98	1.00	0.83	0.44
rs11549907	NA	NT	NT	NT
rs875725	0.00	1.00	1.46	0.18
rs2187776	1.26	0.22	1.55	0.15
rs4821480	0.92	0.79	1.07	0.78
rs2032487	NA	NT	NT	NT
rs4821481	0.89	0.70	1.32	0.16
rs3752462	1.28	0.50	1.10	0.64
rs5756152	1.36	0.11	1.32	0.48
rs1557539	— ^b	—	0.50	0.16
rs1005570	0.62	0.02	0.86	0.55
rs16996674	0.87	0.45	0.61	0.30
rs16996677	0.87	0.51	0.81	0.57
Haplotype				
E-1	1.10	0.80	1.20	0.38
E-2	1.04	0.92	0.98	1.00
E-3	0.87	0.52	1.71	0.71
E-4	0.50	0.04	—	—
E-5	1.21	0.71	—	—

^aNot tested. ^bGenotype missing for both cases and controls for this analysis.