

Methods

DNA was extracted from buffy coats using Qiagen extraction kits. *GSTM1* gene copy number was estimated using a TaqMan Copy Number Assay (ThermoFisher, Waltham, MA; Hs02575461_cn). Real time PCR were performed in a 5 μ L reaction using manufacturer's protocol with RNase P serving as an internal control. Samples were run in quadruplicate on an Applied Biosystems 7900-HT real-time instrument and scored as 0, 1 or 2 gene copies using Applied Biosystems Copycaller software (version 2.1). Only samples that worked 3 or more times and were always concordant were scored. The inactive *GSTM1* genotype was defined by carriage of the *GSTM1(0)* null allele [i.e. *GSTM1(1/0)* and *GSTM1(0/0)*] while the *GSTM1* active group, by definition, is homozygous for the active allele [*GSTM1(1/1)*]. *APOL1* variant sites were genotyped using custom TaqMan assays (ThermoFisher Scientific, Waltham, MA, USA): rs73885319 (Assay ID-AH20SD1), rs60910145 (Assay ID-AHWR1JA), and rs71785313 (Assay ID-AH1RT7T). The *APOL1* high-risk group was defined by carriage of any two copies of the G1 or G2 haplotypes (i.e. G1/G1, G1/G2, or G2/G2 genotypes). Participants were divided into *GSTM1* inactive and *GSTM1* active groups. Logistic regression was used to describe the association between *GSTM1* inactive genotypes and kidney disease (eGFR <60 and <90 mL/min/1.73m², stage 5 CKD, proteinuria (uPCR >50 mg/mmol) and albuminuria (ACR >3 mg/mmol); likelihood ratio tests were used to assess the strength of association at each level. All statistical analyses were done using STATA v16 (StataCorp, College Station, Tx).

Supplementary references

- S1. Carlsten C, Sagoo GS, Frodsham AJ, *et al.* Glutathione S-transferase M1 (GSTM1) polymorphisms and lung cancer: a literature-based systematic HuGE review and meta-analysis. *American journal of epidemiology* 2008; **167**: 759-774.
- S2. Yang M, Zhao J, Xing L, *et al.* Association between GSTM1 null genotype and coronary artery disease risk: a meta-analysis. *Med Sci Monit* 2014; **20**: 1550-1555.

Figure S1 Distribution of eGFR in participants stratified by *GSTM1* copy number, overall (A) and in those with *APOL1* low-risk (B) and high-risk (C) genotypes

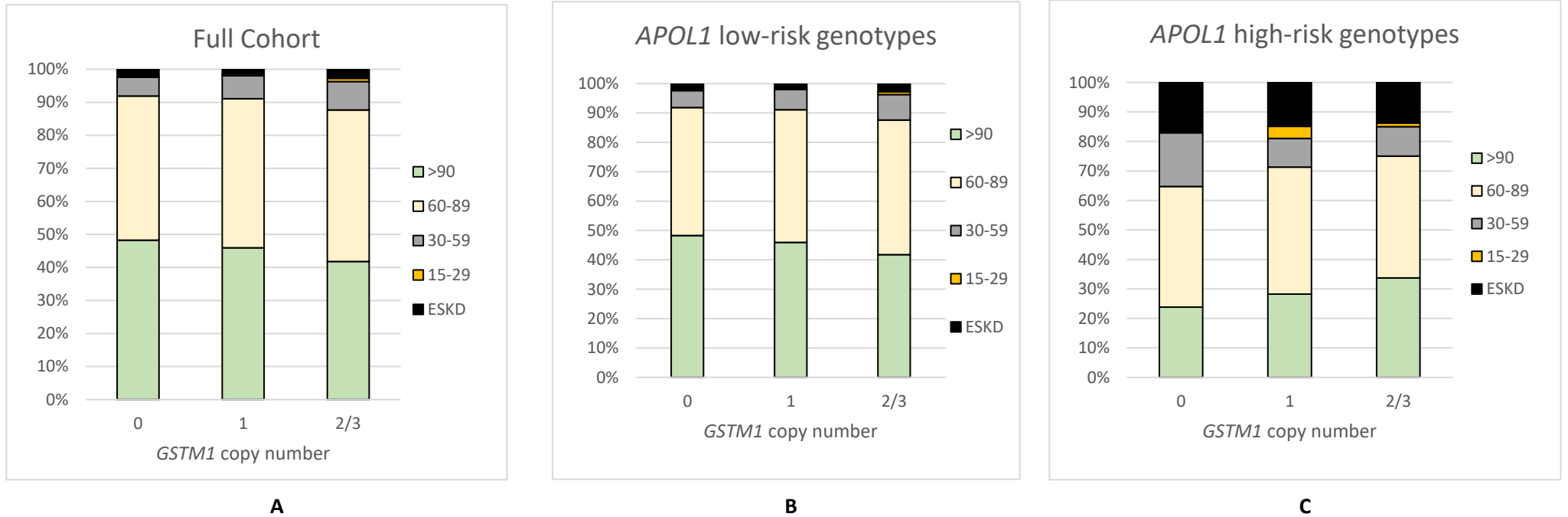


Table S1 Characteristics of study participants stratified by *GSTM1* status

		<i>GSTM1</i> status			p-value
		Total N=2,762	Inactive N=2,075	Active N=687	
Age, years	mean (sd)	48.0 (10.3)	48.0 (10.3)	48.0 (10.2)	0.92
Sex, female	n (%)	1,574 (57.0)	1,190 (57.4)	384 (55.9)	0.5
Region of ancestry					<0.001
East Africa	n (%)	512 (18.5)	430 (20.7)	82 (11.9)	
South Africa	n (%)	735 (26.6)	528 (25.4)	207 (30.1)	
Central Africa	n (%)	154 (5.6)	113 (5.4)	41 (6.0)	
West Africa	n (%)	844 (30.6)	617 (29.7)	227 (33.0)	
Caribbean	n (%)	342 (12.4)	250 (12.0)	92 (13.4)	
Other	n (%)	175 (6.3)	137 (6.6)	38 (5.5)	
HIV mode of acquisition					0.42
Heterosexual	n (%)	2,254 (81.6)	1,686 (81.3)	568 (82.7)	
MSM	n (%)	70 (2.5)	59 (2.8)	11 (1.6)	
Vertical	n (%)	230 (8.3)	174 (8.4)	56 (8.2)	
Blood products	n (%)	22 (0.8)	18 (0.9)	4 (0.6)	
Unknown	n (%)	186 (6.7)	138 (6.7)	48 (7.0)	
Time since HIV diagnosis, years	mean (sd)	13.9 (6.5)	13.9 (6.5)	14.1 (6.2)	0.42
Previous AIDS	n (%)	643 (24.0)	475 (23.7)	168 (25.1)	0.45
Nadir CD4 cell count, cells/mm ³	median (IQR)	200 (80-337)	202 (85-337)	197 (67-341)	0.27
Recent CD4 cell count, cells/mm ³	median (IQR)	560 (399-735)	561.0 (397-730)	558 (407-755)	0.80
On antiretroviral therapy	n (%)	2,731 (98.9)	2,048 (98.7)	683 (99.4)	0.12
HIV RNA <200 copies/mL	n (%)	2,572 (93.1)	1,943 (93.6)	629 (91.6)	0.06
HBsAg positive	n (%)	156 (5.7)	112 (5.5)	44 (6.4)	0.34
Anti-HCV positive	n (%)	37 (1.4)	32 (1.6)	5 (0.7)	0.11
Diabetes	n (%)	273 (10.0)	200 (9.7)	73 (10.7)	0.46
Hypertension	n (%)	884 (32.0)	664 (32.0)	220 (32.0)	0.99
Cardiovascular disease	n (%)	121 (4.4)	93 (4.5)	28 (4.1)	0.65

BMI, kg/m ²					0.59
<18.5	n (%)	22 (0.8)	16 (0.8)	6 (0.9)	
18.5-24.9	n (%)	610 (22.5)	471 (23.1)	139 (20.6)	
25-29.9	n (%)	982 (36.1)	734 (36.0)	248 (36.7)	
≥30	n (%)	1,103 (40.6)	820 (40.2)	283 (41.9)	
Smoking status					0.16
Never	n (%)	2,133 (77.2)	1,586 (76.4)	547 (79.6)	
Ex	n (%)	308 (11.2)	235 (11.3)	73 (10.6)	
Current	n (%)	321 (11.6)	254 (12.2)	67 (9.8)	
eGFR, mL/min/1.73m ²	median (IQR)	86.3 (71.8 - 100.9)	86.5 (71.9 - 101.3)	85.5 (70.9 - 99.2)	0.08
≥90	n (%)	1,194 (43.2)	914 (44.0)	280 (40.8)	0.51
60-89	n (%)	1,232 (44.6)	921 (44.4)	311 (45.3)	
30-59	n (%)	212 (7.7)	151 (7.3)	61 (8.9)	
15-29	n (%)	23 (0.8)	16 (0.8)	7 (1.0)	
<15/RRT	n (%)	101 (3.7)	73 (3.5)	28 (4.1)	
Urine PCR, mg/mmol	median (IQR)	8.5 (6 - 13.3)	8.3 (6 - 13.1)	9 (6.4 - 14)	0.03
<15	n (%)	2,118 (79.6)	1,605 (80.2)	513 (77.8)	0.33
15-49	n (%)	408 (15.3)	300 (15.0)	108 (16.4)	
50-99	n (%)	74 (2.8)	50 (2.5)	24 (3.6)	
≥100	n (%)	61 (2.3)	47 (2.3)	14 (2.1)	
Urine ACR, mg/mmol	median (IQR)	0.7 (0.4 - 1.9)	0.7 (0.4 - 1.8)	0.9 (0.4 - 2.2)	0.002
<3	n (%)	2,107 (82.2)	1,605 (83.1)	502 (79.4)	0.07
3 - 29	n (%)	362 (14.1)	262 (13.6)	100 (15.8)	
≥30	n (%)	94 (3.7)	64 (3.3)	30 (4.7)	
APOL1 genotype					0.10
low-risk	n (%)	2,399 (87.6)	1,792 (87.0)	607 (89.4)	
high-risk	n (%)	339 (12.4)	267 (13.0)	72 (10.6)	
Sickle cell trait	n (%)	331 (12.0)	254 (12.3)	77 (11.3)	0.47

Table S2 Characteristics of study participants stratified by *APOL1* and *GSTM1* status

***APOL1* high-risk genotypes**

		<i>GSTM1</i> status			p-value
		Total	Inactive	Active	
		N=339	N=267	N=72	
Age, years	mean (sd)	47.9 (9.8)	47.8 (9.9)	48.5 (9.5)	0.58
Sex, female	n (%)	179 (52.8)	141 (52.8)	38 (52.8)	0.99
Region of ancestry					
East Africa	n (%)	8 (2.4)	7 (2.6)	1 (1.4)	0.76
South Africa	n (%)	47 (13.9)	37 (13.9)	10 (13.9)	
Central Africa	n (%)	8 (2.4)	7 (2.6)	1 (1.4)	
West Africa	n (%)	216 (63.7)	172 (64.4)	44 (61.1)	
Caribbean	n (%)	49 (14.5)	37 (13.9)	12 (16.7)	
Other	n (%)	11 (3.2)	7 (2.6)	4 (5.6)	
HIV mode of acquisition					
Heterosexual	n (%)				0.36
MSM	n (%)	273 (80.5)	218 (81.6)	55 (76.4)	
Vertical	n (%)	11 (3.2)	9 (3.4)	2 (2.8)	
Blood products	n (%)	27 (8.0)	21 (7.9)	6 (8.3)	
Unknown	n (%)	3 (0.9)	3 (1.1)	0 (0.0)	
Time since HIV diagnosis, years	mean (sd)	25 (7.4)	16 (6.0)	9 (12.5)	
Previous AIDS	n (%)	84 (25.6)	66 (25.3)	18 (26.9)	0.79
Nadir CD4 cell count, cells/mm ³	median (IQR)	188.0 (72.0-315.0)	190.0 (74.0-305.0)	153.5 (42.0-378.0)	0.70
Recent CD4 cell count, cells/mm ³	median (IQR)	541.0 (384.0-705.0)	550.0 (378.0-709.0)	513.0 (389.0-696.5)	0.45
On antiretroviral therapy	n (%)	332 (97.9)	261 (97.8)	71 (98.6)	0.65
HIV RNA <200 copies/mL	n (%)	312 (92.0)	246 (92.1)	66 (91.7)	0.90
HBsAg positive	n (%)	0	17 (6.4)	5 (6.9)	0.88
Anti-HCV positive	n (%)	4 (1.2)	4 (1.5)	0 (0.0)	0.29
Diabetes	n (%)	29 (8.6)	22 (8.3)	7 (9.7)	0.70
Hypertension	n (%)	170 (50.1)	137 (51.3)	33 (45.8)	0.41

Cardiovascular disease	n (%)	20 (5.9)	13 (4.9)	7 (9.7)	0.12
BMI, kg/m ²					
<18.5	n (%)	0	0	0	0.73
18.5-24.9	n (%)	62 (18.8)	51 (19.6)	11 (15.7)	
25-29.9	n (%)	132 (40.0)	102 (39.2)	30 (42.9)	
≥30	n (%)	136 (41.2)	107 (41.2)	29 (41.4)	
Smoking status					0.50
Never	n (%)	276 (81.4)	219 (82.0)	57 (79.2)	
Ex	n (%)	28 (8.3)	23 (8.6)	5 (6.9)	
Current	n (%)	35 (10.3)	25 (9.4)	10 (13.9)	
eGFR, mL/min/1.73m ²	median (IQR)	74.9 (54.5 - 92.1)	73.3 (54.4 - 91.3)	80.9 (55.9 - 93.1)	0.13
≥90	n (%)	92 (27.1)	69 (25.8)	23 (31.9)	0.83
60-89	n (%)	143 (42.2)	114 (42.7)	29 (40.3)	
30-59	n (%)	41 (12.1)	33 (12.4)	8 (11.1)	
15-29	n (%)	9 (2.7)	8 (3.0)	1 (1.4)	
<15/RRT	n (%)	54 (15.9)	43 (16.1)	11 (15.3)	
Urine PCR, mg/mmol	median (IQR)	9.0 (6.0-14.8)	8.5 (6.0-13.0)	11.5 (7.9-20.0)	0.006
<15	n (%)	220 (77.2)	180 (80.4)	40 (65.6)	
15-49	n (%)	44 (15.4)	29 (12.9)	15 (24.6)	
50-99	n (%)	9 (3.2)	4 (1.8)	5 (8.2)	
≥100	n (%)	12 (4.2)	11 (4.9)	1 (1.6)	
Urine ACR, mg/mmol	median (IQR)	1.0 (0.5-3.1)	0.9 (0.4-2.9)	1.0 (0.5-4.7)	0.33
<3	n (%)	207 (74.2)	165 (75.0)	42 (71.2)	
3 - 29	n (%)	49 (17.6)	38 (17.3)	11 (18.6)	
≥30	n (%)	23 (8.2)	17 (7.7)	6 (10.2)	
Sickle cell trait	n (%)	62 (18.3)	53 (19.9)	9 (12.5)	0.15

APOL1 low-risk genotypes

		GSTM1 copies			p-value
		Total	Inactive	Active	
		N=2,399	N=1,792	N=607	
Age, years	mean (sd)	48.0 (10.3)	48.0 (10.4)	48.1 (10.2)	0.83
Sex, female	n (%)	1,386 (57.8%)	1,044 (58.3%)	342 (56.3%)	0.40
Region of ancestry					<0.001
East Africa	n (%)	503 (21.0%)	422 (23.5%)	81 (13.3%)	
South Africa	n (%)	682 (28.4%)	486 (27.1%)	196 (32.3%)	
Central Africa	n (%)	143 (6.0%)	104 (5.8%)	39 (6.4%)	
West Africa	n (%)	620 (25.8%)	442 (24.7%)	178 (29.3%)	
Caribbean	n (%)	289 (12.0%)	209 (11.7%)	80 (13.2%)	
Other	n (%)	162 (6.8%)	129 (7.2%)	33 (5.4%)	
HIV mode of acquisition					0.46
Heterosexual	n (%)	1,960 (81.7%)	1,454 (81.1%)	506 (83.4%)	
MSM	n (%)	58 (2.4%)	49 (2.7%)	9 (1.5%)	
Vertical	n (%)	202 (8.4%)	152 (8.5%)	50 (8.2%)	
Blood products	n (%)	19 (0.8%)	15 (0.8%)	4 (0.7%)	
Unknown	n (%)	160 (6.7%)	122 (6.8%)	38 (6.3%)	
Time since HIV diagnosis, years	mean (sd)	14.1 (6.5)	14.0 (6.6)	14.3 (6.1)	0.39
Previous AIDS	n (%)	552 (23.8%)	404 (23.4%)	148 (24.9%)	0.46
Nadir CD4 cell count, cells/mm ³	median (IQR)	203.0 (83.0-339.0)	205.0 (87.0-341.0)	199.0 (70.0-335.0)	0.32
Recent CD4 cell count, cells/mm ³	median (IQR)	563.0 (402.5-740.0)	562.0 (400.0-734.0)	568.0 (411.0-757.0)	0.60
On antiretroviral therapy	n (%)	2,375 (99.0%)	1,771 (98.8%)	604 (99.5%)	0.15
HIV RNA <200 copies/mL	n (%)	2,237 (93.2%)	1,681 (93.8%)	556 (91.6%)	0.06
HBsAg positive	n (%)	131 (5.5%)	92 (5.2%)	39 (6.5%)	0.24
Anti-HCV positive	n (%)	30 (1.3%)	26 (1.5%)	4 (0.7%)	0.13
Diabetes	n (%)	243 (10.2%)	177 (10.0%)	66 (11.0%)	0.49
Hypertension	n (%)	705 (29.4%)	520 (29.1%)	185 (30.5%)	0.50

Cardiovascular disease	n (%)	0	78 (4.4%)	21 (3.5%)	0.34
BMI, kg/m ²					0.66
<18.5	n (%)	22 (0.9%)	16 (0.9%)	6 (1.0%)	
18.5-24.9	n (%)	541 (22.9%)	415 (23.5%)	126 (21.1%)	
25-29.9	n (%)	844 (35.7%)	628 (35.6%)	216 (36.1%)	
≥30	n (%)	957 (40.5%)	707 (40.0%)	250 (41.8%)	
Smoking status					0.058
Never	n (%)	1,840 (76.7%)	1,356 (75.7%)	484 (79.7%)	
Ex	n (%)	276 (11.5%)	209 (11.7%)	67 (11.0%)	
Current	n (%)	283 (11.8%)	227 (12.7%)	56 (9.2%)	
eGFR, mL/min/1.73m ²	median (IQR)	87.5 (73.9 - 101.4)	88.4 (74.6 - 101.9)	85.9 (71.5 - 99.7)	0.01
≥90	n (%)	1,091 (45.5%)	838 (46.8%)	253 (41.7%)	0.021
60-89	n (%)	1,079 (45.0%)	801 (44.7%)	278 (45.8%)	
30-59	n (%)	169 (7.0%)	116 (6.5%)	53 (8.7%)	
15-29	n (%)	14 (0.6%)	8 (0.4%)	6 (1.0%)	
<15/RRT	n (%)	46 (1.9%)	29 (1.6%)	17 (2.8%)	
Urine PCR, mg/mmol	median (IQR)	8.5 (6.0-13.3)	8.3 (6.0-13.2)	8.8 (6.2-13.8)	0.15
<15	n (%)	1,880 (79.9)	1,413 (80.1)	467 (79.2)	0.88
15-49	n (%)	361 (15.3)	269 (15.3)	92 (15.6)	
50-99	n (%)	65 (2.8)	46 (2.6)	19 (3.2)	
≥100	n (%)	47 (2.0)	35 (2.0)	12 (2.0)	
Urine ACR, mg/mmol	median (IQR)	0.7 (0.4-1.7)	0.7 (0.4-1.6)	0.8 (0.4-2.0)	0.004
<3	n (%)	1,884 (83.2)	1,429 (84.1)	455 (80.4)	0.074
3 - 29	n (%)	310 (13.7)	223 (13.1)	87 (15.4)	
≥30	n (%)	71 (3.1)	47 (2.8)	24 (4.2)	
Sickle cell trait	n (%)	267 (11.2%)	201 (11.3%)	66 (10.9%)	0.80

Appendix

Genetic markers of chronic kidney disease in people of African ancestry with HIV (GEN-AFRICA) Study Group

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