APOL1 VARIANTS, SICKLE CELL TRAIT, AND KIDNEY FAILURE IN AFRICANS WITH HIV

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Background

In people of African ancestry

- Chronic kidney disease (CKD) is a leading cause of morbidity and mortality, and CKD is more likely to progress to end stage kidney disease (ESKD) as compared to Caucasians (1).
- Genetic susceptibility to CKD and ESKD is conferred by two *Apolipoprotein L1* (*APOL1*) risk alleles (2) and by sickle cell trait (SCT) (3).
- The proportion of CKD and ESKD that is attributable to *APOL1* risk alleles and SCT in people of African ancestry with HIV has not been determined.

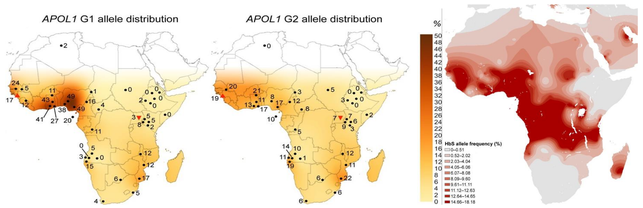


Figure 1 : Prevalence of *APOL1* risk alleles (4) and Sickle Cell Trait (5)

Aims

To analyse the relationship between *APOL1* risk alleles, SCT and kidney disease in people of sub-Saharan African and Caribbean ancestry with HIV in the United Kingdom.

Methods

Study design and data source

- Cross sectional study of adults of black ethnicity receiving routine HIV care in the UK; participants were enrolled between 05/2018 and 02/2020 and provided blood/urine samples for genetic analysis (*APOL1* G1/G2 risk alleles and SCT) and assessment of renal function (estimated glomerular filtration rate [eGFR], urine albumin/creatinine ratio (ACR).

Exposures, outcomes and covariates

Exposures	1. *APOL1* renal-risk genotypes (G1/G1, G1/G2 or G2/G2) 2. Sickle Cell Trait (Hemoglobin AS)
Primary Outcome	ESKD, defined as an eGFR <15 mL/min/1.73m² or receiving permanent renal replacement therapy (RRT)
Secondary Outcomes	CKD (eGFR<60 mL/min/1.73m²) Albuminuria (ACR >3 mg/mmol in those without ESKD)

Variables:

Renal Risk Factors	Hypertension (clinical diagnosis and treatment, or blood pressure >140/>90 mm Hg), diabetes mellitus, and cardiovascular disease (CVD; composite of myocardial infarction, heart failure, coronary artery disease, stroke, peripheral vascular disease), body mass index (BMI)
Demographics	Age, gender, sexual orientation
HIV measures	Prior AIDS, CD4 cell count, HIV viral load
Co-infections	Hepatitis B (surface antigen +), hepatitis C (antibody +)

Analysis

1. We performed logistic regression analysis to describe the associations between ESKD, CKD, albuminuria and *APOL1* renal risk genotypes/SCT.
2. We estimated the population of ESKD attributable to *APOL1* high-risk genotypes and SCT as population attributable risks (PAR): PAR = Pe (RRe-1)/1+Pe (RRe-1) x 100, where Pe was the prevalence of the exposure and RRe was the relative risk of the disease because of the exposure.

Results

A total of 2,895 participants were included: 354 with *APOL1* renal-risk genotypes and 335 with SCT.

Table 1 : Baseline demographics and variables by *APOL1* and SCT status

			APOL1 renal-risk status			Sickle Cell Trait status		
		Total	Low-risk	High-risk	p-value	No SCT	SCT	p-value
		N=2,895	N=2,510	N=354		N=2,560	N=335	
Age, years	Mean (SD)	48.1 (10.3)	48.1 (10.3)	48.2 (10.0)	0.97	48.1 (10.3)	48.3 (10.2)	0.70
Sex, female	N (%)	1,655 (57.2)	1455 (58.0)	186 (52.5)	0.05	1,473 (57.6)	182 (54.3)	0.26
Region of ancestry					<0.001			<0.001
East Africa	N (%)	550 (19.0)	543 (21.6)	11 (3.1)		492 (19.2)	58 (17.3)	
South Africa	N (%)	779 (26.9)	713 (28.4)	52 (14.7)		744 (29.1)	35 (10.4)	
Central Africa	N (%)	160 (5.5)	148 (5.9)	9 (2.5)		126 (4.9)	34 (10.1)	
West Africa	N (%)	865 (29.9)	640 (25.5)	219 (61.9)		711 (27.8)	154 (46.0)	
Caribbean	N (%)	355 (12.3)	297 (11.8)	50 (14.1)		317 (12.4)	38 (11.3)	
Other	N (%)	186 (6.4)	169 (6.7)	13 (3.7)		170 (6.6)	16 (4.8)	
Time since HIV diagnosis, years	Mean (SD)	14.0 (6.5)	14.1 (6.6)	12.8 (6.4)	<0.001	14.0 (6.5)	13.6 (6.6)	0.28
Previous AIDS	N (%)	675 (24.0)	579 (23.1)	86 (25.1)	0.59	599 (24.2)	76 (23.2)	0.72
Nadir CD4 cell count, cells/mm³	Median (IQR)	202 (80-341)	206 (90-337)	185 (70-315)	0.41	208 (84-342)	170 (47-336)	0.027
Recent CD4 cell count, cells/mm³	Median (IQR)	560 (401-733)	569 (408-744)	542 (388-703)	0.14	566 (409-738)	511 (366-692)	0.002
On antiretroviral therapy	N (%)	2,864 (98.9)	2485 (99.0)	347 (98.0)	0.19	2,534 (99.0)	330 (98.5)	0.43
HIV RNA <200 copies/mL	N (%)	2,696 (93.1)	2342 (93.3)	327 (92.4)	0.06	2,393 (93.5)	303 (90.4)	0.04
Hepatitis B (HBsAg)	N (%)	164 (5.7)	135 (5.4)	24 (6.9)	0.05	145 (5.7)	19 (5.8)	0.99
Hepatitis C (anti-HCV)	N (%)	39 (1.4)	31 (1.2)	4 (1.2)	0.28	37 (1.5)	2 (0.6)	0.21
Diabetes	N (%)	291 (10.1)	252 (10.0)	34 (9.7)	0.1	258 (10.2)	33 (10.0)	0.91
Hypertension	N (%)	929 (32.1)	740 (29.5)	175 (49.4)	<0.001	808 (31.6)	121 (36.1)	0.10
Cardiovascular disease	N (%)	130 (4.5)	102 (4.1)	21 (5.9)	0.26	109 (4.3)	21 (6.3)	0.10

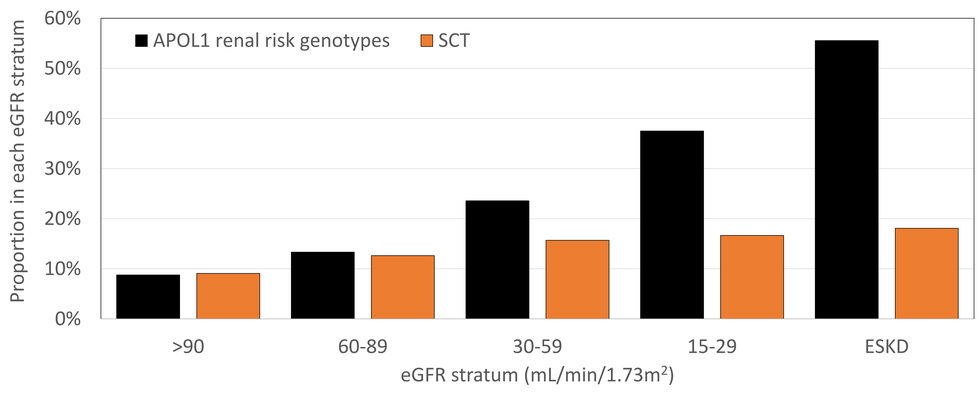
Prevalence of Kidney Disease

Kidney disease was more prevalent among those with *APOL1* renal-risk genotypes and those with SCT.

Table 2 : Prevalence [N (%)] of kidney disease by *APOL1* and SCT status

		APOL1 renal-risk status			Sickle Cell Trait status		
	Overall	Low-risk	High-risk	p-value	No SCT	SCT	p-value
ESKD	102 (3.5)	44 (1.7)	55 (15.5)	<0.001	83 (3.2)	19 (5.7)	0.023
CKD	226 (7.8)	135 (5.4)	86 (24.3)	<0.001	187 (7.2)	39 (11.7)	0.005
Albuminuria	474 (16.4)	399 (15.9)	75 (21.2)	<0.001	399 (16.8)	73 (23.7)	0.004

Prevalence of *APOL1* renal-risk genotypes and SCT in those with and without CKD/ESKD



Odds of Kidney Disease

APOL1 renal-risk genotypes and SCT were associated with ESKD, CKD and albuminuria; the associations were minimally affected by adjustment for demographic, HIV and renal risk factors.

Table 3: Crude and adjusted odd ratios for ESKD, CKD and albuminuria

	OR [95%CI]	P value	aOR* [95%CI]	P value
ESKD				
***APOL1* renal-risk (vs. low-risk) genotypes**	**10.31 (6.81-15.60)**	**<0.001**	**10.58 (6.22-17.99)**	**<0.001**
SCT (vs. no SCT)	**1.79 (1.08-2.99)**	**0.03**	**1.89 (1.03-3.48)**	**0.04**
CKD				
***APOL1* renal-risk (vs. low-risk) genotypes**	**5.65 (4.19-7.61)**	**<0.001**	**5.50 (3.81-7.95)**	**<0.001**
SCT (vs. no SCT)	**1.67 (1.16-2.41)**	**0.006**	**1.81 (1.18-2.78)**	**0.007**
Albuminuria				
***APOL1* renal-risk (vs. low-risk) genotypes**	**1.70 (1.28-2.26)**	**<0.001**	**1.97 (1.46-2.66)**	**<0.001**
SCT (vs. no SCT)	**1.54 (1.16-2.05)**	**0.003**	**1.48 (1.08-2.03)**	**0.01**

* adjusted for age, sex, region of ancestry, prior AIDS, current/nadir CD4 cell count, anti-HCV positive, diabetes and cardiovascular disease

ESKD attributable to *APOL1* renal-risk genotypes and SCT

In this cohort, 49.4% of ESKD was attributable to *APOL1* renal-risk genotypes. In the 2,510 participants with *APOL1* low-risk genotypes, 10.7% of ESKD was attributable to SCT.

Discussion

- *APOL1* renal-risk genotypes were associated with 10-fold odds of ESKD; these genotypes are strongly associated with HIV-associated nephropathy (HIVAN) and focal and segmental glomerulosclerosis (FSGS), and their high prevalence (55%) in participants with ESKD is consistent with the poor renal outcome of these pathologies.
- *APOL1* renal-risk genotypes, HIVAN/FSGS, CKD and ESKD are particularly prevalent in people of West-African (Nigerian and Ghanaian) ancestry; early ART initiation and suppression of HIV replication are likely to confer substantial renal benefit.
- SCT, generally considered to be benign, was associated with 1.5-2 fold odds albuminuria, CKD and ESKD.

Conclusion

APOL1 renal-risk genotypes and SCT are predictors of kidney disease in people of African ancestry with well controlled HIV. Over half of ESKD in this population was attributable to these genetic variants. Novel therapies, especially those targeting the *APOL1* pathway, have the potential to substantially reduce the burden of ESKD in people of African ancestry with HIV, and their evaluation in this population should be prioritized.

References

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