International Journal of
Health, Medicine and Nursing Practice
(IJHMNP)

Association between *APOL 1* Risk Genotypes and Left Ventricular Hypertrophy among Sub-Saharan Africans in *Trypanosoma Brucei Gambiense* Endemic Rural Area

CARI Journals

International Journal of Health, Medicine and Nursing Practice
ISSN 2710-1150 (Online)
Vol.6, Issue No.5, pp 19 - 36, 2024
www.carijournals.org

Association between *APOL 1* Risk Genotypes and Left Ventricular Hypertrophy among Sub-Saharan Africans in *Trypanosoma Brucei Gambiense* Endemic Rural Area

Dominique M. Mupepe[1*], Nathan B. Buila [1], Hippolyte N. Situakibanza [2], Pépé M. Ekulu [3], Marie-Noelle N.L. Wameso [4], Agathe B. Nkoy [3], Exode S. Nsimba [1], Victoire A. Bikoumou [5], Kevin L. Karume [6], Jean Marie N. Kayembe [7], Lambertus P. Van den Heuvel [8], Elena N. Levtchenko [8], Eleuthère V. Kintoki [1], Benjamin M. Longo [1], Dieudonné N. Mumba [2], Jean René M'Buyamba – Kabangu [1].

[1]Division of Cardiology, Department of Internal Medicine, University Hospital of Kinshasa, University of Kinshasa; Kinshasa 11 The Democratic Republic of the Congo (DRC).
[2]Service of Infectious and Parasitic Pathologies, Department of Tropical Medicine, University Hospital of Kinshasa, University of Kinshasa. (DRC).
[3]Pediatric Nephrology Unit, Department of Pediatrics, University Hospital of Kinshasa, University of Kinshasa (DRC).
[4]Service of Nephrology, Department of Internal Medicine, University Hospital of Kinshasa
[5]Department of Radiology and medical imaging, University Hospital of Kinshasa, University of Kinshasa
[6]National Institute of Biomedical Research (INRB), Kinshasa, Democratic Republic of the Congo.
[7]Service of Pneumology, Department of Internal Medicine, University Hospital of Kinshasa, University of Kinshasa (DRC).
[8]Department of Development and Regeneration, KU Leuven, B 3000 Leuven, Belgium
https://orcid.org/0009-0000-5071-9759

Accepted: 4th Apr 2024 Received in Revised Form: 4th May 2024 Published: 4th Jun 2024

Abstract

Purpose. The relationship between *APOL1* variants and cardiovascular disease remains controversial, thus, this study assessed the association between *APOL1* high-risk genotypes and left ventricular hypertrophy (LVH) among sub-Saharan African in *T.b. gambiense* endemic area.

Methodology. We enrolled 238 subjects living in the region of Masimanimba, an endemic area of *T.b.gambiense* HAT. We evaluated the association between LVH on echocardiography and the status of *APOL1* genes in participants with or without HAT. *APOL1* high-risk genotype (HRG) was defined as the presence of two risk variants (G1/G1, G2/G2, or G1/G2), and a low-risk genotype (LRG) with the presence of 0 or 1 single variant. Student's and Pearson's Chi^2 tests or Fisher's exact test were used to compare means and proportions. The Wilcoxon/Mann–Whitney test was used to compare medians. A multivariate logistic regression model was used to identify independent determinants of LVH. Odds ratios were provided with their 95% confidence intervals (Cis). Statistical significance was set at $p < 0.05$, based on 2-tailed test.

Findings. The prevalence of LVH (31.5%) increased with age and was similar in HAT-infected and non-infected subjects (29.8% vs. 32.6%; p=0.376). The trend of a greater left ventricular mass in participants with LVH carrying *APOL1* HRG compared to those with LRG was not statistically significant (141g/m^2 vs. 125 g/m^2; p = 0.253). The frequency of HRG among participants with LVH was similar between HAT-infected and non-infected (15.8% vs. 9.1%; p = 0.806). Age ≥ 38 years [OR 2.5 (95% CI: 1.4-4.5), p = 0.001], hypertension [OR 2.4 (95% CI: 1.1-5.3), p = 0.034], WHR > 0.5 [OR 2.0 (95% CI: 1.0-3.6), p = 0.018] and CKD [OR 1.7 (95% CI: 1.0-3.0), p = 0.049] were associated with LVH. In multivariable logistic regression analysis age ≥ 38 years was the only independent determinant of LVH [ORa 2.0 (95% CI: 1.1-3.8), p = 0.020].

Unique contribution to theory, practice and policy. An assessment of cardiovascular risk is essential for individuals with LVH carrying *APOL1* HRG in order to benefit from early and appropriate medical intervention. Further larger prospective follow-up survey is required to assess the incidence of LVH in individuals with *APOL1* HRG variants.

Keywords: *APOL1, LVH, Trypanosomiasis Endemic Area, DRC*

Introduction

Previous reports have established the relationship between *APOL1* risk variants and CKD in African Americans (AA) and sub-Saharan Africans (1-10). However, this is not the case for subclinical and clinical cardiovascular diseases (CVD) for which the data are contradictory. Indeed, some studies demonstrated a positive correlation, while others observed no significant correlation (11-14). This disparity would be linked to the difference in methodological approaches and the genetic heritage of AA who constitute a mixed population having approximately 80% of African ancestry and 20% of European ancestry (11,14). The lack of available data on *APOL1* variants and CVD in sub-Saharan Africa requires continued research to clarify this relationship where human African trypanosomiasis (HAT) is endemic. Sub-Saharan Africans would not have the same susceptibility to CVD as AA, knowing that these variants do not confer protection against *Tb gambiense* which is prevalent in West and Central Africa (2-4). Therefore, we aimed to investigate the association between *APOL1* risk variants and left ventricular hypertrophy (LVH) in a sample of the Bantu population in a *Tb gambiense* endemic area, in Central Africa.

Methods

Study Design and participant sampling

We conducted this cross-sectional study from April 2019 to April 2021 in an HAT-endemic rural region of Masimanimba (Democratic Republic of Congo (DRC)), where the inhabitants belong to the Bantu ethnic group. A total of 238 individuals aged 15 years or older were enrolled using a multi-stage sampling strategy. They were accrued from two Health Zones in the region: Masimanimba and Mosango. Ten Health areas (six in Masimanimba and four in Mosango) were randomly selected. The enrolment included only subjects justifying a stay of at least one year in the region. Pregnant women were excluded from this study.

Clinical measurements

Sociodemographic data (age, sex, ethnicity, and occupation) and history of cardiovascular risk factors (hypertension, diabetes, tobacco and alcohol use, and low vegetable and fruit consumption) were obtained through interviews. Anthropometric variables (height, weight, waist circumference, and body mass index), blood pressure, and heart rate were measured during the physical examination. Brachial and ankle blood pressure was measured using an automated sphygmomanometer (Omron M2 Basic (HEM-7120-E), Kyoto, Japan) with an appropriate size secured on each arm and ankle in turn after the subject had rested in the supine position for at least 5 min. The average of three measurements at 1 min intervals was used in the analysis. Pulse pressure (PP) is the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). The ankle-brachial index (ABI) was calculated as the ratio of the highest systolic blood pressure at the two ankles to the highest systolic blood pressure at the two arms.

Paraclinical and genetic variables assessment

Laboratory variables (serum creatinine, glucose, total cholesterol, HDL and LDL- cholesterol, uric acid, C-reactive protein (CRP), and triglycerides) were measured with a Cobas C 111 analyzer

using an enzymatic colorimetric method at the National Institute for Biomedical Research (NIBR). Estimated glomerular filtration rate (eGFR) was calculated using the MDRD (Modification of Diet in Renal Disease) formula: The albumin/creatinine ratio in freshly voided morning urine samples was evaluated. CKD was an eGFR < 60mL/min/1.73 m^2 and/or a urinary albumin/creatinine ratio ≥ 30 mg/g persistent for ≥ 3 months (15). HAT was diagnosed using serological [card agglutination test for trypanosomiasis (CATT)] and parasitological tests [mini anion exchange column (mAECT)].

DNA was extracted from whole blood samples according to the Maxwell method, following the manufacturer's instructions at the Genetics Laboratory of the National Institute for Biomedical Research (INRB). The extracted DNA was transferred to the Laboratory of Development and Regeneration at Katholieke University, Leuven (KU Leuven, Belgium) for storage and genotyping. APOL1 genotyping was performed for two renal risk alleles: G1 (coding variants rs73885319A>G [p.Ser342Gly] and rs60910145G>T [p.Ile384Met]) and G2 (6-bp deletion, rs71785313). Exon 7 (883 bp) of APOL1 was amplified using the gene-specific primer pairs (Fw50-GTCACTGAGCCAATCTCAGC-30 and Rv50-CATATCTCTCCTGGTGGCTG-30). Polymerase chain reaction experiments were performed on genomic DNA using GoTaq Green DNA Polymerase (Promega Corporation, Fitchburg, Wisconsin) and consisted of 35 cycles at an annealing temperature of 55º C. Alkaline phosphatase and exonuclease exoSAP IT (Affymetrix, Santa Clara, CA) were used for polymerase chain reaction purification. Sanger sequencing was performed on an ABI 3100XL High-Throughput DNA Sequencer (Applied Biosystems, Foster City, CA, USA). APOL1 HRG was defined as the presence of two risk alleles (G1/G1, G2/G2, or G1/G2), and LRG was defined as the presence of zero or one risk allele.

Echocardiographic measurements

Detailed two-dimensional transthoracic echocardiography was performed using an EDAN echocardiograph (D-20537, Hamburg, Germany) outfitted with a 3.5 MHz transducer. Left ventricle measurements were performed according to the 2015 American Society of Echocardiography and European Association of Cardiovascular Imaging updated guidelines for cardiac chamber quantification (16). Two-dimensional guided M-mode echocardiography was performed in the parasternal long-axis view. The interventricular septum (IVS) thickness in diastole (IVSd) in mm, left ventricular posterior wall (PW) thickness in diastole (LVPWd) in mm, and left ventricular end-diastolic diameter (LVEDd) in mm were measured at end-diastole just below the mitral valve leaflets. ECG was simultaneously recorded at the same time to correlate the measurements with the cardiac cycle. Diastolic wall thickness was measured at the onset of the QRS complex. Left ventricular mass (LVM) was calculated according to the American Society of Echocardiography simplified cubed equation linear method using the following equation: LVM (grams) = $0.8 \times 1.04 \times [(LVEDd + IVSd + LVPWd)^3 - (LVEDd)^3] + 0.6$ g. LVM was indexed to the BSA and height. LVM was considered high when ≥ 115 g/m^2 or ≥ 48 g/m^2 in males and ≥ 95 g/m^2 or ≥ 44 g/m^2 in females. The relative wall thickness (RWT) of the left ventricle (LV) was calculated as (2 × LVPWd)/LVEDd. LV geometric patterns were defined as follows: normal

geometry (normal LVM and RWT ≤ 0.43), concentric remodeling (normal LVM and RWT > 0.43), and concentric hypertrophy (high LVM and RWT > 0.43), and eccentric hypertrophy (High LVM and RWT ≤ 0.43). To assess LV systolic function, ejection fraction (stroke volume/diastolic volume × 100), percentage of LV systolic shortening (%) ([diastolic diameter − systolic diameter]/diastolic diameter × 100], and cardiac output (stroke volume × heart rate) were calculated. The images were stored for subsequent validation by two cardiologists.

Operational definitions

High blood pressure was SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or use of antihypertensive drug treatment (17). Prehypertension was SBP of 120-139 mmHg and a DBP of 80-89 mmHg. (18). An abnormal ankle-brachial index (SBP ankle/SBP arm) < 0.9 or > 1.3 (19) determined a high cardiovascular risk.

Height (in meters) was measured using a flexible tape measure with the participants in an upright position without shoes. Body weight was measured using a digital scale (EKS, Germany), and body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). Overweight was defined as BMI of 25 to 29.9 kg/m^2 and obesity as BMI of 30 kg/m^2 (20). A tape measure was used to measure the waist circumference at the top of the hip bone. Central obesity was defined as waist circumference ≥ 94 cm in men and ≥ 80 cm in women (20). High cardiometabolic risk was defined as a waist-to-height ratio ≥ 0.5 (21)

HAT-infected participants were positive for both serological and parasitological tests and a CATT plasma dilution ≥ 1/8, parasitology negative; non-infected participants had negative or positive CATT plasma dilution < 1/8.

Diabetes mellitus was a fasting serum glucose ≥ 126 mg/dl or use of antidiabetic medication (20). Dyslipidemia was defined as total cholesterol level > 1.9 g/L, triglycerides > 1.5 g/L, and HDL-cholesterol < 0.4 g/l for males and < 0.5 g/l for females) (22). Metabolic syndrome was defined according to IDF/AHA/ NHLBI (2009) by the presence of 3 out of the following 5 criteria: waist circumference ≥ 94 cm in males and ≥ 80 cm in females, - SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg or use of antihypertensive drug treatment, serum triglycerides ≥ 1.5 g/L, HDL-C < 0.40 g/L for males and < 50 g/L for females, fasting serum glucose ≥ 100 mg/dl or use of antidiabetic medication (20). C-reactive protein level > 6 mg/L was considered an inflammatory marker (23). Anemia was defined as hemoglobin (Hb) level of < 12.0 g/dl in women and < 13.0 g/dl in men (24). Elevated uric acid was considered when blood levels were > 6 mg/dl or 360 µmol/L (25)

Statistical analysis

Data analysis was performed using SPSS for Windows software version 21. Student's and Pearson's Chi^2 tests or Fisher's exact test were used to compare means and proportions, where appropriate. The Wilcoxon/Mann–Whitney test was used to compare medians. A multivariate logistic regression model was used to identify independent determinants of left ventricular Hypertrophy (LVH). Odds ratios were provided with their 95% confidence intervals (Cis).

Statistical significance was set at $p < 0.05$, based on 2-tailed test. A chi-squared test was used to test the deviation from Hardy-Weinberg equilibrium.

Results

General Characteristics of the study population

As shown in Table 1, the prevalence of LVH was 31.5% and increased with age ($p = 0.002$). It was similar in males (30%) and females (32%) ($p = 0.404$), in HAT-infected (29.8%) as well as non-infected (32.6%) individuals ($p = 0.376$). Participants with LVH were older than those without LVH (46.5 vs. 36.5 years; $p < 0.001$).

Table 1: General Characteristics of the study population

Characteristics	**All** **N = 238**	**With LVH** **N = 75 (31,5)**	**Without LVH** **N = 163 (68,5)**	**p value**
Age, years	39.7 ± 17.1	46.5 ± 17.1	36.5 ± 16.1	**< 0,001**
HAT status				0.376
Infected	94 (39.4)	28 (29.8)	66 (70.2)	
Non-Infected	144 (60.6)	47 (32.6)	97 (67.3)	
Sex				0.404
Male	90 (37.9)	27 (30)	63(70)	
Female	148 (62.1)	48 (32.4)	100 (67.6)	
Age groups				**0.002**
< 20	29 (12.2)	4 (13.8)	25 (86.2)	
20-29	46 (19.3)	10 (21.7)	36 (78.3)	
30-39	53 (22.3)	12 (22.6)	41 (77.4)	
40-49	38 (16)	16 (42.1)	22 (57.9)	
≥ 50	72 (30.3)	33 (45.8)	39 (54.2)	

Data are expressed as mean ± SD or absolute (n) and relative (%) frequency HAT = human African trypanosomiasis

LVH = left ventricular hypertrophy

Distribution of Cardiovascular risk factors and *APOL1* risk genotypes by LVH status

The distribution of cardiovascular risk factors in participants with and without LVH is shown in Table 2. Participants with LVH demonstrated high frequency of hypertension (20% vs. 9.2%, p = 0.019), WHR ≥ 0.5 (34.7% vs. 20.9%, p = 0.018) and CKD (53.3% vs. 39.3%; p = 0.029), while an abnormal ABI was noted in participants without LVH (33.7% vs. 20%, p = 0.021). The other variables did not differ between the two groups.

APOL1 sequence analysis showed that four of 30 (13.3%) participants with LVH and six of 94 (6.4%) participants without LVH carried HRG; the difference between the two groups was not significant (p = 0.253). Participants in both groups carried G1G1, G2G2, and G1G2 genotypes. The trend of G1 (20% vs. 15.4%, p = 0.427) and G2 (11.7% vs. 8%, p = 0.434) alleles to be slightly higher in the subjects with than those without LVH was not significant.

Table 2: Distribution of Cardiovascular risk factors and *APOL1* risk genotypes by LVH status

Cardiovascular risk factors	**All N = 238**	**With LVH N = 75 (31,5)**	**Without LVH N = 163 (68,5)**	p **value**
Low consumption of fruits	231 (97)	74 (98.7)	157 (96.3)	0.295
Dyslipidemia	191 (80.2)	56 (74.7)	135 (82.8)	0.099
Alcohol intake	178 (74.7)	59 (78.7)	119 (73)	0.221
Low consumption of vegetables	111 (46.6)	30 (40)	81 (49.7)	0.105
CKD	104 (43.6)	40 (53.3)	64 (39.3)	**0.029**
Tachycardia	102 (42.8)	31 (41.3)	71 (43.6)	0.429
Smoking	88 (36.9)	33 (44)	55 (33.7)	0.085
Albuminuria	79 (33.1)	28 (37.3)	51 (31.3)	0.219
Abnormal ABI	70 (29.4)	15 (20)	55 (33.7)	**0.021**
Prehypertension	66 (27.7)	20 (26.7)	46 (28.2)	0.466
WHR ≥ 0.5	60 (25.2)	26 (34.7)	34 (20.9)	**0.018**
Inflammation	56 (23.5)	20 (26.7)	36 (22.1)	0.269
Hyperuricemia	39 (16.3)	12 (16)	27 (16.6)	0.538
Hypertension	30 (12.6)	15 (20)	15 (9.2)	**0.019**
Abdominal Obesity	28 (11.7)	12 (16)	16 (9.8)	0.124
Diabetes	9 (3.7)	2 (2.7)	7 (4.3)	0.420
Overweight - obesity	7 (2.9)	3 (4)	4 (2.5)	0.387
Metabolic Syndrome	6 (2.5)	1 (1.3)	5 (3,1)	0.386
***APOL1* risk variants**	**N = 124**	**With LVH n=30**	**Without LVH N = 94**	**P value**
At least one allele risk	53 (42.7)	15 (50)	38 (40.4)	0.400
High-risk genotypes	10 (8.1)	4 (13.3)	6 (6.4)	0.253
G1/G1	5 (4)	2 (6.7)	3 (3.2)	
G2/G2	2 (1.6)	1 (1.1)	1 (3.3)	
G1/G2	3 (2.4)	1 (3.3)	2 (2.1)	
Low-risk genotypes	114 (91.9)	26 (86.7)	88 (93.6)	0.253
G1/G0	28 (22.6)	7 (23.3)	21 (22.3)	
G2/G0	15 (12.1)	4 (13.3)	11 (11.7)	
G0/G0	71 (57.3)	15 (50)	56 (59.6)	
****Alleles**				
G1	41(16.5%)	12 (20)	29 (15.4)	0.427
G2	22 (8.8%)	7 (11.7)	15 (8)	0.434

Data are expressed as mean ± SD or absolute (n) and relative (%) frequency ABI = Ankle brachial index

WHR = Waist Height ratio CKD = chronic kidney disease LVH = left ventricular hypertrophy

** considering all chromosomes.

Cardiovascular risk factors in the study population by HAT infection status.

The distribution of cardiovascular risk factors according to HAT infection status is shown in Table 3 for participants with and without LVH. HAT-uninfected subjects were older than the infected ones among participants with LVH (49.6 vs. 41.4 years, p = 0.047) as well as those without (38.1 vs. 34.1 years, p = 0.123). Men were more susceptible to HAT infection than women (p = 0.045). Albuminuria predominated in HAT-infected subjects with LVH (57.1% vs. 25.5%, p = 0.006). The frequency of HRG was similar between HAT-infected patients with and without LVH (15.8 vs. 9.1%, p = 0.806). Among participants without LVH, diabetes (9.1% vs. 1%, p = 0.018), dyslipidemia (93.9% vs. 75.3%, p = 0.001), prehypertension (39.4% vs. 20.6%, p = 0.008), hypertension (16.7% vs. 4.1%, p = 0.008), and anemia (50% vs. 26.8%, p = 0.002) predominated in HAT-infected subjects. The trend towards a higher HRG frequency in HAT-infected patients was not significant (9.6% vs. 2.4%, p = 0.220).

Table 3: Distribution of cardiovascular risk factors by HAT infection status

Cardiovascular risk factors	**All** **N = 238**	**With LVH** **N = 75**			**Without LVH** **N = 163**		
		HAT$^+$ **n=28**	**HAT$^-$** **n=47**	**p**	**HAT$^+$** **n=66**	**HAT$^-$** **n=97**	**p**
Age (Yrs)	39.7 ± 17.1	41.4 ± 18.6	49.6±15.7	**0.047**	34.1±15.6	38.1±16.4	0.123
Sex				**0.045**			0.096
Male	90 (37.8)	14 (50)	13 (27.7)		30 (45.5)	33 (34)	
Female	148 (62.2)	14 (50)	34 (72.3)		36 (54.5)	64 (66)	
Smoking	88 (36.9)	12 (42.9)	21 (44.7)	0.535	12 (18.2)	43 (44.3)	**< 0.001**
Alcohol intake	178 (74.7)	22 (78.6)	37 (78.7)	0.603	52 (78.8)	67 (69.1)	0.116
Low fruit consumption	231 (97)	28 (100)	46 (97.9)	0.627	65 (98.5)	92 (94.8)	0.221
Low vegetable consumption	111 (46.6)	8 (28.6)	22 (46.8)	0.093	30 (45.5)	51 (52.6)	0.232
Diabetes	9 (3.7)	1 (3.6)	1 (2.1)	0.610	6 (9.1)	1 (1)	**0.018**
Dyslipidemia	191 (80.2)	24 (85.7)	32 (68.1)	0.075	62 (93.9)	73 (75.3)	**0.001**
Metabolic syndrome	6 (2.5)	0 (0)	1 (2.1)	0.627	4 (6.1)	1 (1)	0.087
prehypertension	66 (27.7)	9 (32.1)	11 (23.4)	0.286	26 (39.4)	20 (20.6)	**0.008**
Hypertension	30 (12.6)	5 (17.9)	10 (21.3)	0.483	11 (16.7)	4 (4.1)	**0.008**
Hyperuricemia	39 (16.3)	5 (17.9)	7 (14.9)	0.487	11 (16.7)	16 (16.5)	0.570
Abnormal ABI	70 (29.4)	5 (17.9)	10 (21.3)	0.483	18 (27.3)	37 (38.1)	0.101
Overweight-Obesity	7 (2.9)	0 (0)	3 (6.4)	0.240	1 (1.5)	3 (3.1)	0.466
Abdominal Obesity	28 (11.7)	2 (7.1)	10 (21.3)	0.096	8 (8.2)	8 (12.1)	0.289
WHR ≥ 0.5	60 (25.2)	7 (25)	19 (40.4)	0.134	13 (19.7)	21 (21.6)	0.461
Anemia	88 (36.9)	13 (46.4)	16 (34)	0.206	33 (50)	26 (26.8)	**0.002**
Inflammation	56 (23.5)	8 (28.6)	12 (25.5)	0.488	16 (24.2)	20 (20.6)	0.359
Microalbuminuria	79 (33.1)	16 (57.1)	12 (25.5)	**0.006**	17 (25.8)	34 (35.1)	0.139
Tachycardia	102 (42.8)	11 (39.3)	20 (42.6)	0.487	27 (40.9)	44 (45.4)	0.344
Chronic Kidney Disease	104 (43.6)	18 (64.3)	22 (46.8)	0.109	25 (37.9)	39 (40.2)	0.447
APOL1 risk variants	**N = 124**	**N = 19**	**N = 11**		**N = 52**	**N = 42**	
High-risk genotypes	10 (8.1)	3 (15.8)	1 (9.1)	0.806	5 (9.6)	1 (2.4)	0.220
G1/G1	5 (4)	1 (5.3)	1 (9.1)		3 (5.8)	0 (0)	
G2/G2	2 (1.6)	1 (5.3)	0 (0)		1 (1.9)	0 (0)	
G1/G2	3 (2.4)	1 (5.3)	0 (0)		1 (1.9)	1 (2.4)	
0 risk allele	71 (57,3)	9 (47.4)	6 (54.5)	0.858	32 (61.5)	24 (57.1)	0.234
G0/G0	71 (57.3)	9 (47.4)	6 (54.5)		32 (61.5)	24 (57.1)	
1 risk allele	43 (34,7)	7 (36.8)	4 (36.4)	0.852	15 (28.8)	17 (40.5)	0.210
G1/G0	28 (22.6)	5 (26.3)	2 (18.2)		9 (17.3)	12 (28.6)	
G2/G0	15 (12.1)	2 (10.5)	2 (18.2)		6 (11.5)	5 (11.9)	

Data are expressed as mean ± SD or absolute (n) and relative (%) frequency ABI = Ankle brachial index WHR = Waist Height ratio LVH = left ventricular hypertrophy HAT+ = infected HAT - = non-infected

Participants' characteristics by *APOL1* genotypes status.

Table 4 indicates that 4/30 (13.3%) subjects who carried *APOL1* HRG had higher means for all components of blood pressure (SBP, DBP, MAP, and PP), anthropometric parameters (WC, IMC, WHR), and left ventricular mass (LVM) than 26 of 30 (86.7%) subjects with LRG. However, the difference was significant only for the PP (p = 0.047). Moreover, subjects with LVH carrying HRG had an elevated median urinary ACR (p = 0.008) and LDL-C (p = 0.029). Participants without LVH who carried the HRG had a higher median u-ACR (p < 0.001) and glycaemia (p < 0,001) than those who carried the LRG. However, it should be noted that all individuals with or without LVH carrying the HRG had significant albuminuria.

Tableau 4: Clinical and paraclinical characteristics of participants by *APOL1* genotype status.

	All n = 124	**With LVH n = 30**			**Without LVH n = 94**		
		HRG n = 4	**LRG n = 26**	**p**	**HRG n = 6**	**LRG n = 88**	**p value**
Age (Yrs)	38.3 ± 17	48 ± 20	47.6 ± 19.8	0.977	49.3 ± 13.3	34.4 ± 14.7	**0.019**
Gender				0.177			0.173
Male	51 (41.1)	0 (0)	10 (38.5)		1 (16.7)	40 (45.5)	
Female	73 (58.9)	4 (100)	16 (61.5)		5 (83.3)	48 (54.5)	
SBP (mm Hg)	119.5 ± 19.9	151.2 ± 53.4	121.2 ± 24.3	0.063	126.5 ± 26.7	117.1 ± 13.9	0.139
DBP (mm Hg)	74.1 ± 14	90 ± 26.6	76.1 ± 17	0.170	74.8 ± 18.7	72.7 ± 11.6	0.690
MAP ((mm Hg)	89.2±15.5	110.2 ± 35.6	91.5 ± 19.4	0.125	90.5 ± 25.2	87.5 ± 11.8	0.650
PP ((mm Hg)	45.4 ± 11,2	61.2 ± 27.1	44.9 ± 12.2	**0.047**	51.5 ± 19.5	44.4 ± 8.5	0.080
abnormal ABI	1.1 ± 0.3	1.2 ± 0.5	1 ± 0.2	0.359	1 ± 0.1	1.1 ± 0.3	0.371
WC (cm)	72.9 ± 6.7	80 ± 10,7	75 ± 5.8	0.167	73.8 ± 4.6	71.9 ± 6.7	0.513
BMI (Kg/m^2)	19 ± 2.7	21.5 ± 3.1	19.7 ± 2.1	0.168	19 ± 3.2	18.7 ± 2.7	0.822
WHR≥ 0.5	0.4 ± 0.2	0.6 ± 0.5	0.4 ± 0.3	0.465	0.3 ± 0.2	0.3 ± 0.2	0.239
LVM (g/ m^2 de BS)	93.5 ± 25.8	141 ± 31.5	125.1 ± 24.4	0.253	78.6 ± 11.1	83 ± 14.3	0.462
HR (batt /min)	79.1 ± 14.6	86.7 ± 22	79.3 ± 16.4	0.425	82.3 ± 13.1	78.5 ± 14	0.517
Fasting serum glucose (mg/dl)	78 [55-93]	76.5	77.5	0.880	111.5	78	**<0.001**
Total Cholestérol (mg/dl)	73.6 ± 33	86.2 ± 34.9	67.4 ± 27.1	0.222	68 ± 33.8	75.2 ± 34.6	0.619
HDL-c (mg/dl)	26.8 ± 14.7	22 ± 10.1	26.5 ± 16.4	0.595	19.5 ± 10.1	27.6 ± 14.6	0.184
LDL-c (mg/dl)	41.8 ± 29.3	61.5 ± 26.8	35.3 ± 20.3	**0.029**	44 ± 27.3	42.6 ± 31.6	0.922
Triglycerides (mg/dl)	46.5 ± 26.8	26.7 ± 14.6	46.7 ± 26.3	0.152	50.6 ± 20.1	47.1 ± 27.7	0.760
uricemia (mg/dl)	6.1 ± 3.1	5.5 ± 0.5	6.3 ± 2.8	0.561	6.5 ± 2.5	6.1 ± 3.4	0.781
CRP (g/L)	7 ± 1.9	8.3 ± 1.7	2 ± 0.8	0.293	7.3 ± 1.9	6.8 ± 0.9	0.912
Hematocrit (%)	39.2 ± 6.4	40.5 ± 5.8	38.7 ± 5.8	0.586	37.1 ± 5.8	39. 4 ±6.7	0.426
U-ACR (mg/g)	28 [12-72]	47	24	**0.008**	36.5	18.5	**< 0,001**
eGFR , mL/min/ 1.73 m^2	108.7 ± 48.2	69 ± 12.7	107.3 ± 43.9	0.098	84.8 ± 25.6	112.5 ± 50.6	0.189
CKD n (%)	54 (43.5)	4 (100)	16 (61.5)	0.272	6 (100)	28 (31.8)	**0,002**

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; ABI, ankle-brachial index; WHR, waist circumference: height ratio; WC, waist circumference; BMI, body mass index; HR, heart rate; CRP, C-reactive protein; U-ACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate. CKD, chronic kidney disease; HRG, high-risk genotype; LRG, low-risk genotype; LVH, left ventricular hypertrophy; LVM, left ventricular mass.

Determinants of LVH in the study population

As reported in Table 5, univariate analysis showed that age ≥ 38 years [OR 2.5 (1.4-4.5), p = 0.001], hypertension [OR 2.4 (1.1-5.3), p = 0.034], WHR ≥ 0.5 [OR 2.0 (1.0-3.6), p = 0.018] and CKD [OR 1.7 (1.0-3.0), p = 0.049,] were associated with LVH. Multivariate logistic regression analysis revealed that age ≥ 38 years was the primary independent factor associated with LVH. Age ≥ 38 years was associated with a two-fold increased susceptibility to LVH [OR 2.0 (1.1-3.8), p = 0.020].

Table 5. Determinants of LVH in the study population

Variables	Univariate Analysis		Multivariate Analysis	
	OR [CI 95%]	p	OR [CI 95%]	p value
Age (yrs)				
< 38	**1**		**1**	
≥ 38	**2.5 [1.4-4.5]**	**0.001**	**2.0 [1.1-3.8]**	**0.020**
Gender				
Female	1		1	
Male	0.8 [0.5-1.5]	0.404	0.9 [0.5-1.8]	0.951
Hypertension				
No	**1**		1	
Yes	**2.4 [1.1-5.3]**	**0.034**	1.9 [0.8-4.6]	0.113
HAT status				
Non-infected	1		1	
Infected	0.8 [0.4-1.5]	0.376	1.0 [0.5-1.9]	0.810
Overweight-obesity				
No	1		1	
Yes	1.6 [0.3-7.5]	0.387	0.9 [0.1-5.2]	0.926
Abdominal obesity				
No	1		1	-
Yes	1.7 [0.7-3.9]	0.195	1.3 [0.5-3.4]	0.534
WHR≥0.5				
Non	**1**		1	
Oui	**2.0 (1.0-3.6)**	**0.018**	1.2 (0.5-2.8)	0.654
Dyslipidemia				
No	1		1	
Yes	0.6 [0.3-1.1]	0.099	0.6 [0.3-1.3]	0.227
Albuminuria				
No	1		1	
Yes	1.3 [0.7-2.3]	0.219	0.7 [0.2-1.7]	0.459
Chronic Kidney Disease				
No	1		1	
Yes	**1.7 [1.0-3.0]**	**0.049**	1.9 [0.7-5.0]	0.151
APOL1 risk Genotypes				
Low (0,1)	1		1	
High (2)	2.2 [0.5-8.6]	0.198	0.7 [0.1-3.7]	0.717

OR, odds ratio; CI, confidence interval; WHR, waist-to-height ratio; HAT=Human African Trypanosomiasis.

Discussion

This study aimed to investigate the possible association between *APOL1* risk variants with LVH in a sample of the Bantu population in a *T. b. gambiense* endemic area. Salient points in the results

were a similar prevalence of LVH in HTA-infected and-uninfected participants. The presence of hypertension, albuminuria, and CKD, but not *APOL1* HRG, was associated with LVH.

Clinical and paraclinical characteristics

LVH was observed in one of three subjects. It increased with age and was similar in HTA-infected and uninfected participants. The two groups of participants exhibited a similar frequency of *APOL1* HRG, probably because these variants do not confer protection against *T.b. gambiense* (26). Our results indicated higher blood pressure, pulse pressure and anthropometric measurements in subjects with LVH who carried an HRG than in those carrying an LRG. The observed association of age ≥ 38 years, hypertension, WHR > 0.5, and CKD with LVH is consistent with the literature, which reports that age and blood pressure (BP) are the main determinants of vascular remodeling (27). The stiffness of the large arterial trunks contributes to the elevation of pulse pressure, which is a factor in the development of LVH (28), as well as greater intima-media thickness of large-caliber arteries and arterioles (29,30). Remodeling of small arteries results in an increase in peripheral resistance and, thus, in mean arterial pressure. In turn, arterial stiffness increases BP and central pulse pressure, which are remodeling factors for LVH. High and uncontrolled BP leads to vascular structural and functional modifications associated with neuro-hormonal, molecular, and genetic factors that cause LVH. However, LVH also occurs in the general population of patients with coronary disease, obesity, and diabetes mellitus (31,32).

Although these factors are known to contribute to LVH development, a high prevalence of diabetes, prehypertension, hypertension, and anemia was observed in HAT-infected participants without LVH. Such an observation could be accounted for by the somewhat higher frequency of *APOL1* HRG in HAT-infected individuals than in non-infected individuals. Our findings are consistent with previous reports that *APOL1* HRG is associated with increased SBP, albuminuria, and CKD (11,33-38). One should bear in mind, however, that subclinical nephropathy can manifest as increased blood pressure (11,33,34,36), and CKD can be the cause of anemia. Finally, an association between serum level of *APOL1* and insulin resistance (HOMA-IR) has been reported to underlie the occurrence of diabetes mellitus (39).

Determinants of LVH

Our results showed a similar prevalence of LVH in both HAT-infected and-uninfected subjects with a similar frequency of HRG. Individuals with LVH who carried the HRG had high u-ACR and decreased eGFR and risk of CKD, although *APOL1* HRG was not associated with LVH. Age ≥ 38 years emerged as the only independent correlate of LVH in the *T.b. gambiense* endemic area. Several studies have established that *APOL1* HRG is not associated with LVH in AA (33,34,40), although HRG carriage has been strongly associated with albuminuria and/or CKD (2,5,11), which are predictors of LVH (37,38,41). Subclinical CKD is a risk factor for CVD, particularly persons of African descent (42); it is known that albuminuria and reduced GFR independently increase the risk of subclinical and clinical cardiovascular events. Therefore, it is difficult to attribute increased cardiovascular risk only to the *APOL1* G1/G2 risk alleles (43). The «Jackson Heart Study (JHS) », a prospective cohort study, showed a positive association between *APOL1* HRG and incident CVD,

including myocardial infarction, stroke, cardiac surgery, and arterial catheterization, but not LVH, despite the presence of diabetes in some individuals (34). In contrast, the «Systolic Blood Pressure Intervention Trial «SPRINT» (33), a randomized multicenter study, did not show any association between *APOL1* HRG and the prevalence of CVD (including myocardial infarction; coronary revascularization; carotid endarterectomy or carotid stenting; peripheral arterial disease with revascularization; 50% stenosis of a coronary, carotid, or lower extremity artery; abdominal aortic aneurysm ≥ 5 cm with or without repair; coronary artery calcium score ≥ 400 Agatston units; ankle-brachial index ≤ 0.90; and left ventricular hypertrophy). Some authors have identified diabetes and prior CKD as strong risk factors that may obscure any independent effects of *APOL1* risk genotypes. Thus, *APOL1* has neutral or protective effects in the presence of diabetes (44,45).

The present study is the first to investigate a possible association between *APOL1* HRG and CVD in sub-Saharan African living in a rural area endemic to *T. b. gambiense*. However, owing to its cross-sectional design we could not ascertain the cause-and-effect nature of any observed relationship. Moreover, the relatively small sample size does not allow for generalization of the findings.

Conclusion

LVH is more prevalent in areas of DRC endemic for *T.b. gambiense*. The prevalence was similar in HAT-infected and uninfected participants, with a similar frequency *of APOL1* HRG. Only age ≥ 38 years emerged as an independent factor for LVH in *T. b. gambiense* endemic areas. An assessment of cardiovascular risk is essential for individuals with LVH carrying *APOL1* HRG in order to benefit from early and appropriate medical intervention. Therefore, a larger prospective follow-up survey is required to assess the incidence of LVH in individuals with *APOL1* HRG variants.

References

1. Atta MG , Estrella M.M, Kuperman M, Foy M.C, Fine DM, Racusen L.C, et al. HIV-Associated nephropathy patients with and without apolipoprotein L1 gene variants have similar clinical and histological characteristics. Kidney Int. 2012; 82(3): 338 – 43.
2. Genovese G., Friedman D.J., Ross M.D., Lecordier L., Uzureau P., Freedman B.I., et al. Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans. Science 2010. 329 (5993): 841–845.
3. Friedman DJ and Pollak MR. Genetics of kidney failure and the evolving story of apol1. J Clin Invest. 2011; 121(9):3367–74.
4. Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P. et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol 2011; 22 (11): 2129–2137.

5.Tzur S, Rosset S, Shemer R, Yudkovsky G, Selig S, Tarekegn A et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum Genet. 2010; 128:345–350.

6.Larsen CP, Beggs ML, Saeed M, Walker PD. Apolipoprotein L1 risk variants associate with systemic lupus erythematosus-associated collapsing glomerulopathy. J Am Soc Nephrol. 2013; 24 (5):722–725.

7.Ashley-Koch AE, Okocha EC, Garrett ME, Soldano K., De Castro LM, Jonassaint JC et al. MYH9 and APOL1 are both associated with sickle cell disease nephropathy. Br J Haematol. 2011; 155 (3):386–394.

8.Freedman BI, Langefeld CD, Andringa KK, Croker JA, Williams AH, Garner NE, et al. End-stage kidney disease in African Americans with lupus nephritis associates with APOL1. Arthritis Rheumatol 2014; 66(2):390-6. doi: 10.1002/art.38220.

9.Tayo BO, Kramer H, Salako BL,Omri Gottesman, Colin A McKenzie, Adesola Ogunniyi, et al. Genetic variation in APOL1 and MYH9 genes is associated with chronic kidney disease among Nigerians. Int Urol Nephrol. 2013, 45(2): 485-94.

10. Ulasi II, Tzur S, Wasser WG, Shemer R, Kruzel E, Feigin E, et al. High population frequencies of APOL1 risk variants are associated with increased prevalence of non-diabetic chronic kidney disease in the Igbo people from south-eastern Nigeria. Nephron Clin Pract. 2013; 123(1-2):123-8. doi: 10.1159/000353223. Epub 2013 Jul 13. PMID: 23860441

11. McLean N.O, Robinson T.W, Freedman B.I. APOL1 Gene Kidney Risk Variants and Cardiovascular Disease: Getting to the Heart of the Matter. Am J Kidney Dis. 2017; 70(2): 281–289. doi:10.1053/j.ajkd.2016.11.020

12. Reiner AP, Susztak K. APOL1 Variants: From Parasites to Kidney Function to Cardiovascular Disease. Arterioscler Thromb Vasc Biol. 2016; 36(2):219–220. [PubMed: 26819463]

13. Farrall M. Cardiovascular twist to the rapidly evolving apolipoprotein L1 story. Circ Res. 2014; 114(5):746–747. [PubMed: 24577959]

14. Lipkowitz MS. Apolipoprotein L1: from obscurity to consistency to controversy. Kidney Int 2015; 87: 14-17.

15. KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. Suppl. 2013, 3(1): 1 – 160.

16. Lang RM, Badano LP , Mor-Avi V , Afilalo J , Armstrong A, Ernande L, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging, 2015. 16(3): p. 233-70

17. Varagic J, Susic D, Frolich E. Heart, aging and hypertension. Curr Opin Cardiol. 2001, 16: 336-41.

18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JJ et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289:2560–2572.

19. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation. 2004; 109(6):733-9. doi: 10.1161/01.CIR.0000112642.63927.54. PMID: 14970108.

20. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA et al. Harmonizing the Metabolic Syndrome. A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120 (16): 1640-45

21. Browning L, Hsieh S, Ashwell M. A Systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes could be a suitable global boundary value. Nutr Res Rev 2010; 23: 247-69

22. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34):3227-3337. doi: 10.1093/eurheartj/ehab484. Erratum in: Eur Heart J. 2022 Nov 7;43(42):4468. PMID: 34458905.

23. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int 1999; 55: 1899-911.

24. World Health Organization .Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011, World Health Organization. https://apps.who.int/iris/handle/10665/85839

25. Kerola T, Kauppi J, Sares-Jäske L, Anttonen O, Junttila MJ, Huikuri HV et al. Long-term prognostic impact of hyperuricemia in community. Scand J Clin Lab Invest, 2019. 79(3): p. 148-153.

26. Cooper A, Ilboudo H, Alibu VP, Ravel S, Enyaru J, Weir W et al. *APOL1* renal risk variants have contrasting resistance and susceptibility associations with African trypanosomiasis. Elife. 2017; 6:e25461. doi: 10.7554/eLife.25461. PMID: 28537557; PMCID: PMC5495568.

27. Mulvany MJ, Baumbach GL, Aalkjaer C, Heagerty AM, Korsgaard N, Schiffrin EL, et al.. Vascular remodeling. Hypertension. 1996; 28(3):505-6. PMID: 8794840.

28. Boutouyrie P, Laurent S, Girerd X, Benetos A, Lacolley P, Abergel E et al.. Common carotid artery stiffness and patterns of left ventricular hypertrophy in hypertensive patients. Hypertension. 1995; 25(4 Pt 1):651-9. doi: 10.1161/01.hyp.25.4.651. PMID: 7721411.

29. Bussy C, Boutouyrie P, Lacolley P, Challande P, Laurent S. Intrinsic stiffness of the carotid arterial wall material in essential hypertensives. Hypertension. 2000; 35(5):1049-54. doi: 10.1161/01.hyp.35.5.1049. PMID: 10818063.

30. Boutouyrie P, Bussy C, Lacolley P, Girerd X, Laloux B, et al. Association between local pulse pressure, mean blood pressure, and large-artery remodeling. Circulation. 1999;100(13):1387-93. doi: 10.1161/01.cir.100.13.1387. PMID: 10500038
31. Cuspidi C, Mancia G, Ambrosioni E, Pessina A, Trimarco B, Zanchetti A; APROS Investigators. Left ventricular and carotid structure in untreated, uncomplicated essential hypertension: results from the Assessment Prognostic Risk Observational Survey (APROS). J Hum Hypertens. 2004;18(12):891-6. doi: 10.1038/sj.jhh.1001759. PMID: 15284833.
32. Mancia G, Carugo S, Grassi G, Lanzarotti A, Schiavina R, Cesana G, et al; Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) Study. Prevalence of left ventricular hypertrophy in hypertensive patients without and with blood pressure control: data from the PAMELA population. Pressioni Arteriose Monitorate E Loro Associazioni. Hypertension. 2002;39(3):744-9. doi: 10.1161/hy0302.104669. PMID: 11897756.
33. Langefeld CD, Divers J, Pajewski NM, Hawfield AT, Reboussin DM, Bild DE, et al; Systolic Blood Pressure Intervention Trial (SPRINT). Apolipoprotein L1 gene variants associate with prevalent kidney but not prevalent cardiovascular disease in the Systolic Blood Pressure Intervention Trial. Kidney Int. 2015; 87(1):169-75. doi: 10.1038/ki.2014.254. Epub 2014 Jul 16. PMID: 25029429; PMCID: PMC4281289.
34. Ito K, Bick AG, Flannick J, Friedman DJ, Genovese G, Parfenov MG, et al. Increased burden of cardiovascular disease in carriers of APOL1 genetic variants. Circ Res. 2014; 114(5):845-50. doi: 10.1161/CIRCRESAHA.114.302347. Epub 2013 Dec 30. PMID: 24379297; PMCID: PMC3982584.
35. Nadkarni GN, Galarneau G, Ellis SB, Nadukuru R, Zhang J, Scott SA et al. Apolipoprotein L1 Variants and Blood Pressure Traits in African Americans. J Am Coll Cardiol. 2017; 69(12): 1564–1574. doi: 10.1016/j.jacc.2017.01.040
36. Freedman BI, Murea M. Target organ damage in African American hypertension: role of APOL1. Curr Hypertens Rep. 2012; 14:21–8. [PubMed: 22068337]).
37. Wannamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. Stroke. 1997;28(3):557-63. doi: 10.1161/01.str.28.3.557. PMID: 9056611.
38. McCullough PA, Jurkovitz CT, Pergola PE, McGill JB, Brown WW, Collins AJ, et al, for the KEEP Investigators. Independent Components of Chronic Kidney Disease as a Cardiovascular Risk State: Results From the Kidney Early Evaluation Program (KEEP). Arch. Intern. Med. 2007; 167(11):1122–1129. [PubMed: 17563019].
39. Nishimura K, Murakami T, Sakurai T, Miyoshi M, Kurahashi K, Kishi S, et al. Circulating Apolipoprotein L1 is associated with insulin resistance-induced abnormal lipid metabolism. Sci Rep. 2019;9(1):14869. doi: 10.1038/s41598-019-51367-7.
40. Gutiérrez OM, Limou S, Lin F, Peralta CA, Kramer HJ, Carr JJ et al. APOL1 nephropathy risk variants do not associate with subclinical atherosclerosis or left ventricular mass in middle-aged black adults. Kidney Int. 2018;93:727–732. doi: 10.1016/j.kint.2017.08.019

41. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001; 134(8):629–636. [PubMed: 11304102]

42. Pollak MR, Genovese G, Friedman DJ. *APOL1* and kidney disease. Curr Opin Nephrol Hypertens. 2012; 21 (2):179–182.

43. Kruzel-Davila E, Walter GW, Aviram S, Skorecki K. *APOL1* nephropathy: from gene to mechanisms of kidney injury. Nephrol Dial Transplant 2016; 31 (3): 349–358 doi: 10.1093/ndt/gfu391.

44. Gutiérrez OM, Irvin MR, Ninad S. Chaudhary NS, Cushman M, Zakai NA, David VA et al. APOL1 nephropathy risk variants and incident cardio-vascular disease events in community-dwelling black adults. Circ Genom Precis Med. 2018;11:e002098. doi: 10.1161/CIRCGEN.117.002098.

45. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005;25:135– 143. doi: 10.1159/000086678