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Original Article

G1 and G2 variants of apolipoprotein L1 among Central African population in *Trypanosoma brucei gambiense* endemic rural area

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Abstract

Introduction: Apolipoprotein L1 (*APOL1*) risk variants (*G1*, *G2*) are known to enhance the protective ability against human African trypanosomiasis (HAT), in addition to their role in kidney and cardiovascular disease. The effects of these variants on trypanosome infection could differ regionally owing to local adaptations of the host and pathogen. This study explored APOL1 risk variants distribution in HAT-infected and non-infected populations from a rural *Trypanosoma brucei gambiense* (*T. b. gambiense*) endemic area in Central Africa.

Methodology: We conducted a cross-sectional study with 124 participants in Masimanimba, a HAT-endemic region in the Democratic Republic of the Congo (DRC). Student's and Pearson's Chi-square test or Fisher's exact tests were used as appropriate. Statistical significance was set at $p < 0.05$, based on two-tailed test.

Results: 71 participants (57%) were infected by *Trypanosoma*, 65 (52%) of whom were symptomatic and 6 (5%) asymptomatic. The overall frequency of risk alleles was 16.5% for G1 and 8.8% for G2. Neither variant was associated with the susceptibility to *T. b. gambiense* infection (for G1: 19.7% vs. 26.4 %; OR: 0.68 [95% CI: 0.29–1.62], $p = 0.394$; for G2: 11.3% vs. 13.2% 0.83 [0.27–2.58], $p = 0.786$). All of the G2 variants were found in symptomatic patients

Conclusions: APOL1 variants are common in populations living in *T. b. gambiense* endemic areas of the DRC. Neither variant was associated with susceptibility to *T. b. gambiense*. The G2 variant was the only one associated with symptomatic HAT.

Key words: APOL1 variants; trypanosomiasis; endemic; DR Congo.

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Introduction

African Americans (AA) carrying *Apolipoprotein L1* (*APOL1*) *G1* (*rs73885319 - S342G, rs60910145 - I384M*) or *G2* (*rs71785313 - D 388:389 NY*) variants have been reported to exhibit an increased susceptibility to cardiovascular disease (CVD) and chronic kidney disease (CKD) compared to other ethnic groups [1–6]. In this regard, individuals who are homozygous (*G1G1*, *G2G2*) or heterozygous (*G1G2*) for the two *APOL1* alleles had an approximately 2–3 times increased risk of CVD and CKD compared to low-risk carriers (1 or 0 allele) [7–9)]. In the United States, approximately 34% of AA carry at least one *APOL1* variant, and 13% carry both the alleles [10–12], whereas only 0.3% and 0.1% of Caucasian Americans carry the *G1* and *G2* alleles, respectively. The *APOL1 G1/G2* variants have been

identified in the sub-Saharan population with a remarkably high cumulative frequency of 22% and 13% respectively for G1 and G2, compared to the Caucasian populations (1%), and confer in vivo resistance to *Trypanosoma brucei rhodesiense* (*T. b. rhodesiense*) [1,13]. However, these variants confer susceptibility or resistance to human African trypanosomiasis (HAT), depending on the *Trypanosoma* species in endemic rural areas. Indeed, the *G2* allele has been reported to reduce susceptibility to *T. b rhodesiense* infection and increase susceptibility to severe *Trypanosoma brucei gambiense* (*T. b. gambiense*) disease [14]. The G1 allele confers resistance against severe *T. b. gambiense* disease [14,15]. The protective or harmful effects of these variants depend on the pathogen, host, and environment in which the individual lives [8,14,15]. The Democratic Republic of the Congo (DRC) is one of the foci of *T. b gambiense* in the world; however, limited data are available on the epidemiology of *APOL1* risk variants in HAT-endemic areas. The present study aimed to assess the association between *APOL1* risk variants and susceptibility to *T. b. gambiense* infection, as well as the association between these variants and the *T. b. gambiense* disease outcomes.

Methodology

Study design and sampling

This cross-sectional study was conducted in the HAT-endemic region of Masimanimba, DRC from April 2019 to August 2021. Participants were enrolled using a multi-stage sampling strategy in Masimanimba and Mosango, two health zones (HZ) with high HAT endemicity. Ten health areas were randomly selected, including 6 in the Masimanimba HZ and 4 in the Mosango HZ, and the inhabitants were identified. Participants aged ≥ 15 years, living in the study area for at least 1 year, who had benefited from HAT screening tests, and consented to participate, were included in the study.

Clinical and paraclinical assessment

Sociodemographic data (e.g., age, gender, and length of stay in the endemic area) were collected from all participants. HAT was diagnosed using the card agglutination test for trypanosomiasis (CATT). When the test was positive, the researchers looked for trypanosomes in aspirates of enlarged cervical lymph nodes. If the result was negative, CATT titration was performed. If the latter proved positive, trypanosomes were extracted from the venous blood using enrichment techniques, namely capillary tube centrifugation and mini anion exchange column (mAECT). Participants classified as HAT-infected were positive for both serological (CATT) and parasitological (mAECT) tests, or had CATT plasma dilution ≥ 1/8, parasitology negative. The individuals maintained this phenotype for at least 2 years (latent carriers). Uninfected participants were negative or had positive CATT plasma dilutions of < 1/8.

Assessment of APOL1 renal risk alleles

DNA was extracted from whole blood samples at the Genetics Laboratory of the National Institute for Biomedical Research (INRB) using the Maxwell method following the manufacturer's instructions (Maxwell16®, Promega, Lyon, France). 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*). The exon 7 (883 bp) of *APOL1* was amplified using the gene-specific primer pairs (Fw50-GTCACTGAGCCAATCTCAGC-30 and Rv50-CATATCTCTCCTGGTGGCTG-30).

Polymerase chain reaction (PCR) was performed on genomic DNA using GoTaq Green DNA polymerase (Promega Corporation, Fitchburg, Wisconsin) and consisted of 35 cycles at an annealing temperature of 55 ºC. Alkaline phosphatase and exonuclease exoSAP IT (Affymetrix, Santa Clara, CA) were used for PCR purification. Sanger sequencing was performed on an ABI 3100XL High-Throughput DNA Sequencer (Applied Biosystems, Foster City, CA, USA). *APOL1* high-risk genotype (HRG) was defined as the presence of two risk alleles (*G1*/*G1*, *G2*/*G2*, or *G1*/*G2*), and low-risk genotype (LRG) was defined as the presence of 0 or 1 risk allele.

Ethics approval

This study was approved by the Ethics Committee of the School of Public Health of the University of Kinshasa (approval no: ESP/CE/087B/2023). All rules of confidentiality were guaranteed by the research team, in compliance with the principles of the Declaration of Helsinki. All participants included in the study or their guardians (for participants under the age of 18 years) provided verbal or written consent.

Statistical analysis

Data analysis was performed using the SPSS for Windows software version 21 (SPSS Inc. Chicago, IL, USA, 2013). Student's and Pearson's Chi-Square test or

Fisher's exact tests were used as appropriate. Odds ratios were provided with their 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$, based on two-tailed test. A Chi-square test was used to test the deviation from Hardy-Weinberg equilibrium.

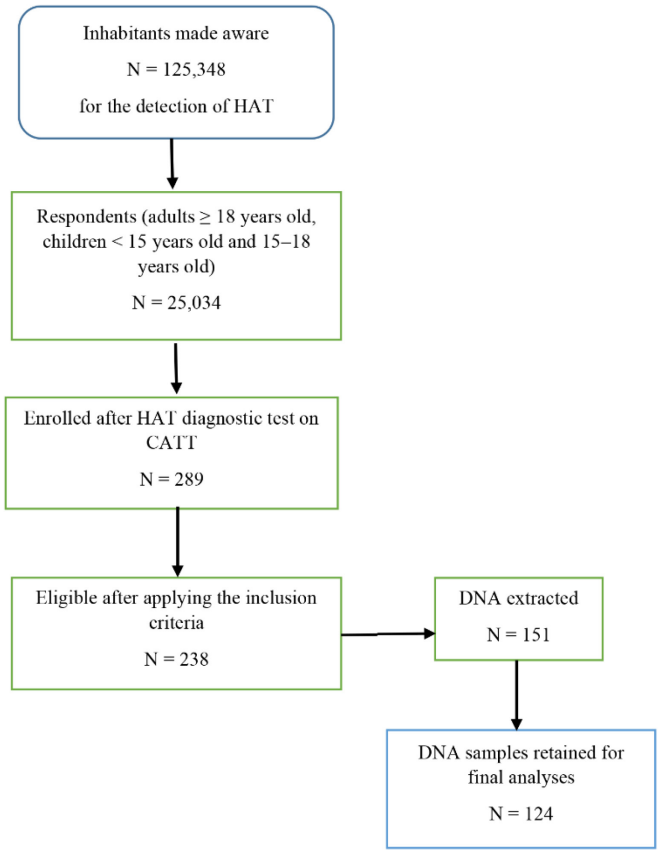
Results

Characteristics of the study population

Figure 1 illustrates the flow of participants in this study. Of the 289 participants enrolled, 238 (82%) met the inclusion criteria; 87 (36.5%) were excluded as they did not present for blood sample collection for the buffy coat. DNA samples were collected from 151 participants. Of these, 27 were discarded due to impurities and/or low yield. Thus, the data of 124 participants, including 73 women (58.9%), with an average age of 38.4 ± 17 years, were retained for the analysis. Seventy-one (57%) participants were infected with *Trypanosoma*, including 65 (52%) symptomatic and 6 (5%) asymptomatic. Fifty-three (43%) participants were uninfected. The average age of the HAT-infected participants was higher than that of the uninfected participants ($p = 0.240$). The general characteristics of the study population is summarized in Table 1. Data are expressed as mean ± SD or absolute (n) and relative frequency (%).

APOL1 sequence analysis revealed that of the 124 participants, 10 (8.1%) carried the HRG, 28 (22.6%) carried the *G1*/*G0* genotype, and 15 (12.1%) the *G2*/*G0* genotype. Considering all chromosomes, the risk allele frequencies were 16.5% and 8.8 % for *G1* and *G2*, respectively. Of the 124 participants, 43 (34.7%) carried one of the *APOL1* variants, and 53 (42.7%) carried at least one risk variant. The prevalence of *G1* and *G2* variants and the frequency of high- and low-risk genotypes were similar in HAT-infected and uninfected participants.

Figure 1. Participants' flow diagram.



HAT: human African trypanosomiasis; CATT: card agglutination test for trypanosomiasis.

Table 1. Characteristics of the study population.

Characteristics	All n = 124	HAT-infected subjects n = 71	Uninfected subjects n = 53	*p* values
Age (years)	38.4 ± 17	36.8 ± 16.7	40.4 ± 17.3	0.240
Gender				
Male	51 (41.1)	26 (36.6)	25 (47.2)	0.159
Female	73 (58.9)	45 (63.4)	28 (52.8)	0.271
At least one allele risk	53 (42.7)	30 (42.3)	23 (43.4)	0.522
High-risk genotype	10 (8.1)	8 (11.3)	2 (3.8)	0.117
G1/G1	5 (4)	4 (5.6)	1 (1.9)	
G2/G2	2 (1.6)	2 (2.8)	0 (0)	
G1/G2	3 (2.4)	2 (2.8)	1 (1.9)	
Low-risk genotype	114 (91.9)	63 (88.7)	51 (96.2)	0.186
G1/G0	28 (22.6)	14 (19.7)	14 (26.4)	
G2/G0	15 (12.1)	8 (11.3)	7 (13.2)	
G0/G0	71 (57.3)	41 (57.7)	30 (56.6)	
Alleles				
G1	41 (16.5%)	24 (16.9%)	17 (16%)	1.000
G2	22 (8.8%)	14 (9.9%)	8 (7.5%)	0.653

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

Association between APOL1 risk variants and susceptibility to T. b. gambiense infection

Neither variant demonstrated any association with susceptibility to *T. b. gambiense* infection when comparing the infected and uninfected participants (Table 2). The frequencies of *G1* and *G2* alleles in both groups were similar (*G1*: 19.7% vs. 26.4%, $p = 0.394$; *G2*: 11.3% vs. 13.2%, $p = 0.786$).

Association between APOL1 risk variants and T. b. gambiense infection outcome

No association was observed between the *APOL1* risk variants and *T. b gambiense* infection outcomes. *APOL1 G1* was not associated with predisposition to latent asymptomatic carriage. While it was not possible to determine the association between *G2* and the development of symptomatic *T. b. gambiense* infection, given the small number of *T. b. gambiense* carriers, the *G2* allele frequency tended to be higher in symptomatic infections (Table 3).

Discussion

In the present study, we assessed the prevalence of *APOL1* risk variants *G1* and *G2* alleles in a rural Congolese population endemic for HAT; as well as the association between these variants and both susceptibility and disease outcome linked to the pathogen *T. b. gambiense.* The salient point in the results was that neither variant was associated with susceptibility to *T. b. gambiense* infection. Although *G2* tended to be more prevalent in symptomatic patients, the *G1* variant was not associated with *T. b. gambiense* infection severity.

Prevalence of APOL1 risk variants

Our results indicate a similar prevalence of *G1* and *G2* among infected and uninfected participants, suggesting that neither variant influences susceptibility to *T. b. gambiense* infection, as reported by previous studies [1,14,15]. The prevalence of *G1* (16.5%) and *G2* (8.8%) in our study population was similar to that reported by Ekulu *et al.* among children in the general population in Kinshasa (12.4% for G1 and 10.4% for G2) [16]. However, it was lower than that observed in other African populations (22% for G1 and 13% for G2) and in African Americans (20% to 22% for G1, and 13% to 15% for G2) [1,8,13]. The G1 allele frequency in our setting was much lower than that observed in West Africa (40%) [3,17]. It has been hypothesized that the *APOL1 G1* allele, and, to a lesser extent, the *G2* allele, have undergone selective scanning in West Africa over the past 10,000 years and are widespread throughout sub-Saharan Africa and the African diaspora [1,8]. Consequently, there would have been a balanced selection of *G1* and *G2* variants in West Africa. The heterozygous form confers protection against trypanosomiasis, whereas the homozygous form is associated with increasing susceptibility to CKD [1,14,24,25]. The high frequency of *APOL1 G1* and *G2* alleles in African Americans could be attributed to the

Table 2. Association between *APOL1* risk variants and susceptibility of *T. b. gambiense* infection.

***APOL1* variants**	**Infected**		**Non-infected**		**Association between infected / non-infected OR [95% CI]**	***p***
	Number	**%**	**Number**	**%**		
G0	63	88.7	51	96.2	0.31 [0.04–1.42]	0.186
Non-G0	8	11.3	2	3.8		
Total	71	100	53	100		
G1	14	19.7	14	26.4	0.68 [0.29–1.62]	0.394
Non-G1	57	80.3	39	73.6		
Total	71	100	53	100		
G2	8	11.3	7	13.2	0.83 [0.27–2.58]	0.786
Non-G2	63	88.7	46	86.8		
Total	71	100	53	100		

Data are expressed as mean ± SD or absolute (n) and relative (%) frequency. CI: confidence interval: OR: odd ratio.

Table 3. Association between *APOL1* risk variants and *T. b. gambiense* infection outcome in HAT-infected patients.

***APOL1* variants**	**Symptomatic patients**		**Asymptomatic patients**		**Association between symptomatic / asymptomatic patients OR [95% CI]**	***p***
	Number	**%**	**Number**	**%**		
G0	59	90.8	4	66.7	4.92 [0.52–33.12]	0.133
Non-G0	6	9.2	2	33.3		
Total	65	100	6	100		
G1	13	20	1	16.7	1.25 [0.16–31.91]	1.000
Non-G1	52	80	5	83.7		
Total	65	100	6	100		
G2	8	12.3	0	0	NC	1.000
Non-G2	57	87.7	6	100		
Total	65	100	6	100		

Data are expressed as mean ± SD or absolute (n) and relative (%) frequency. CI: confidence interval; NC: not calculable; OR: odd ratio.

dispersion of people from West Africa during the Trans-Atlantic slave trade from 16th to 19th centuries [19,20]. For these reasons, the prevalence of *APOL1* HRG (8.1%) in our study population was also lower than that observed in both the African American (10% to 15%) and the West African populations (23% to 28%) [18,21]. Nevertheless, this is consistent with reports in Central Africa, as the Masimanimba population belongs to the Bantu ethnic group that drifted from the Niger-Congo language family, which originates from the neighboring regions of Cameroon and Nigeria [21,26,27].

Association between APOL1 risk variants and susceptibility of T. b. gambiense infection

Our data did not reveal any association between *APOL1* risk *G1* (*rs73885319* - S342G, *rs60910145* - I384M) or *G2* (*rs71785313* - D 388:389 NY) variants and susceptibility to *T. b. gambiense* infection. This observation concurs with surveys performed in the *T. b. gambiense* HAT foci of north-west Uganda [22], and in the mangrove area of coastal Guinea [14]. The ethnic groups in the HAT foci are the Nilo-Saharan family language in Uganda and the Niger-Congo family language in the mangroves of Guinea. This suggests that these variants do not restore trypanolytic activity against *T. b. gambiense,* implying that neither variant confers protection against *Trypanosoma* species [1]. However, divergent results have been reported for *T. b. rhodesiense* infections in different ethnic groups. Indeed, a single copy of the *G2* variant has been shown to be lytic and protective against *T. b. rhodesiense* [1,17]. In Uganda, an association was found between *APOL1 G2* and protection against *T. b. rhodesiense* infection in the Nilo-Saharan family language population; however, no association was detected in the ethnic groups of the Bantu language family [22], whereas the frequency of *G2* was similar in both groups. Conversely, a significant difference in *G1* frequency was observed between the two groups (Bantu 14% vs. Nilo - Saharan 2%) [18]. The *T. b. rhodesiense* and *T. b. gambiense* parasite resistance to human serum is mediated by different mechanisms that place distinct selective pressures on host genes. The effects of these variants on natural infections and the development of acute and chronic HAT are complex and not fully understood [28].

Association between APOL1 risk variants and T. b. gambiense infection outcome

In our study, no association was observed between the *APOL1* risk *G1* variant and predisposition to latent asymptomatic carriage. Determining the association between *G2* and the development of symptomatic *T. b. gambiense* infection proved challenging owing to the low number of *T. b. gambiense* carriers. Therefore, the power of our statistical tests was significantly reduced. Nevertheless, the frequency of the *G2* allele tended to be higher in symptomatic *T. b. gambiense* infections. Studies from HAT-endemic regions of the Sub-Saharan African population found that the *G2* variant was associated with a higher risk of developing *T. b. gambiense* infection, whereas *G1* was associated with a low risk [15]. The *G2* allele, even in the heterozygous state, conferred protection against *T. b. rhodesiense*, and was associated with the development of infection by *T. b. gambiense*. *G1* was associated with asymptomatic *T. b. gambiense* parasitemia [14,15]. In contrast, one study showed no evidence of variants associated with *T. b. rhodesiense* or *T. b. gambiense* HAT in two Ugandan populations exposed to both trypanosome species [22]. The distribution of *APOL1* variants frequencies is complex, and varies among African ethnic groups, even within the same region or country. Therefore, HAT severity may differ owing to local adaptation by the host and the pathogen [23].

The present study has the merit of addressing the prevalence of *APOL1* variants in a rural Central African environment endemic for *T. b. gambiense* HAT. However, the sample size was remarkably small and was accrued from a single and narrow area. Thus, the extent to which the results can be reliably extrapolated to the entire Congolese population is uncertain. Further studies using nationally representative samples are needed to confirm these results.

Conclusions

APOL1 risk variants are common in populations living in rural areas endemic for *T. b. gambiense* in the DRC. Although neither variant was associated with susceptibility to *T. b. gambiense* infection, G2 was associated with symptomatic HAT. Considering the mixed and heterogeneous populations in Africa, this study provides perspectives for other larger genetic surveys.

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Author contributions

Study design: DMM, JRMB-K, HNS, DNM, M-NNLW, JMNK, PME; data collection: DMM, M-NNLW, DNM, RZM, ABN, KLK, LPVdH, ENL; data analysis and interpretation: DMM, VAB, JRMB-K, PME, ABN, KLK, M-NNLW, LPVdH, ENL, DNM; draft writing and revision of manuscript: DMM, JRMB-K, JMNK, HNS, DNM, JRRM, M-NNLW, NBB, PME, BML. All authors have read and approved the final version of this manuscript.

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