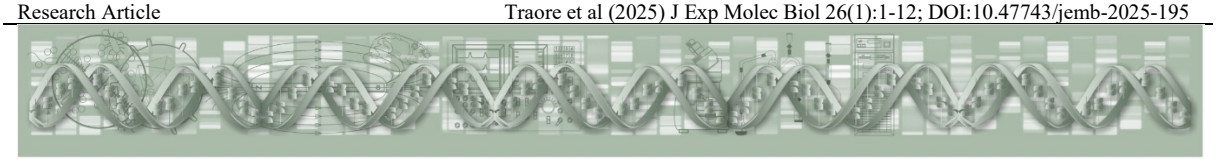

INVOLVEMENT OF HLA-DRB1*11 AND HLA-DRB1*12 ALLELES IN THE OCCURRENCE OF DENGUE FEVER IN BURKINA FASO

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Abstract

Dengue has become the world's most common arbovirosis. In some individuals, genetic factors can increase the risk of developing severe dengue fever. Human leukocyte antigen (HLA) genes are one of human disease's most extensively studied gene groups. The present study investigated HLA DRB1*11 and HLA DRB1*12 polymorphisms in dengue cases and their susceptibilities in developing dengue in a population in Ouagadougou, Burkina Faso. This was a case-control study involving 56 patients with clinically and biologically confirmed dengue fever and 65 others who had never been in contact with DENV, for a total of 121 individuals. A blood sample was taken from each study participant. After extraction of genomic DNA using the salting-out technique, characterization of carriage of the HLA-DRB1*11 and 1*12 alleles was carried out using multiplex polymerase chain reaction (PCR). The χ^2 test, odds ratio (OR), and confidence interval (CI) were calculated using SPSS software to estimate associations and assess the level of risk. Allele frequencies in the general population were 64.4% and 62.8% for HLA DRB1*11 and HLA DRB1*12, respectively. The HLA-DRB1*12 allele was present in 28.9% of cases and 33.9% of controls. The HLA-DRB1*11 allele was present in 32.2% of both cases and controls. In this study, no direct association was found between the presence of the HLA-DRB1*11 and HLA-DRB1*12 alleles and the surveillance of dengue infection. Furthermore, the absence of the HLA-DRB1*11 allele was associated with protection against the development of severe disease (OR = 0.03; 95% CI [0.11 - 0.80]; and p = 0.01). No risk of developing severe dengue fever was found in individuals carrying the HLA-DRB1*11 and HLA-DRB 1*12 alleles. However, further study of other HLA alleles involved in the development of severe dengue may provide more information.

Keywords: Dengue, HLA-DRB1*11, HLA-DRB1*12, risk factors, Burkina Faso

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Background

Dengue is a vector-borne viral infection that occurs mainly in urban areas of the intertropical zone. Once confined to Southeast Asia and the Americas, the disease has progressively spread disproportionately to all WHO regions worldwide. The main dengue vector is Aedes aegypti, followed by Aedes albopictus. The dengue virus (DENV) belongs to the Flavivirus genus of the Flaviviridae family. It is divided into four serotypes: DENV-1 to DENV-4 and causes dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (1). Dengue has become the world's most common arbovirosis (2). In 5 to 30% of confirmed cases, the condition can be severe and complex. The main indicators of disease severity include thrombocytopenia, plasma leakage, haemorrhage and hypovolemic shock, commonly known as DHF and DSS (3). Dengue fever is common in tropical and subtropical regions worldwide, with a predilection for urban and semi-urban areas. The global incidence of dengue has risen dramatically, and half the world's population is now at risk of contracting the disease. Between 100 and 400 million infections are recorded each year worldwide, but only around 20% of these are generally symptomatic (4). The dengue situation in the African region remains relatively undocumented. However, the disease affects several West African countries, including Burkina Faso, particularly its capital Ouagadougou (5).

In some individuals, genetic factors can increase the risk of developing severe dengue fever (2). Human leukocyte antigen (HLA) genes are one of the most studied groups of genes in human disease (3). In humans, HLA molecules are encoded by the major histocompatibility complex (MHC) and are located on chromosome 6. Class I and II molecules are involved in the presentation of peptide antigens to host T cells to activate the immune system. They harbour the most important genetic polymorphisms in the host and play an important role in the selection of target antigens and in determining the nature and intensity of the immune response(1). The MHC carries around 220 genes for proteins, more than half of which are directly involved in immunity.

The genes of the HLA system are organized into three regions: HLA class I, HLA class II and HLA class III. Class I comprises HLA-A, HLA-B and HLA-C, while class II comprises HLA-D and its subtypes HLA-DO, HLA-DP, HLA-DQ and HLA-DR (6). The HLA system has approximately 28,938 alleles, including 21,040 class I alleles and 7,898 class II alleles (7). Numerous studies have revealed that allelic polymorphism in the genes of the HLA system is associated with various diseases. HLA class I molecules are the most studied. As for HLA class II molecules, HLA-DRB and HLA-DQ are the most widely studied genes. Two alleles of the HLA DRB gene, namely: HLA-DRB1*11 and HLA-DRB1*12, are associated with protection against or susceptibility to dengue fever in different populations (8,9). These associations may also vary according to ethnic and geographical distribution (8). To this end, it is important to provide sufficient information on the likely implications of these alleles in the occurrence and/or protection of the host against the severe form of dengue in each endemic region. This will strengthen control strategies and serve as a lead in the production of a possible effective dengue vaccine.

However, there are no known studies in the literature implicating the HLA-DRB1*11 and HLA-DRB1*12 alleles in the development of dengue fever in Burkina Faso. The aim of this study was therefore to determine the association of the HLA-DRB1*11 and HLA-DRB1*12 alleles with the occurrence of dengue fever in the population of Burkina Faso.

Materials and Methods

This study aimed to determine the involvement of the HLA-DRB1*11 and HLA-DRB1*12 alleles in the occurrence of DENV infection and its progression towards severe forms of the disease in Burkina Faso.

This was an analytical case-control study. The study lasted 6 months, i.e., from September 2022 to February 2023. The study population consisted of 122 individuals subdivided into two groups: 57 cases and 65 controls. They included patients of different age groups, including children, and donors representing different professions and social statuses.

Blood samples were taken from three different laboratories, including those at Hôpital Saint Camille de Ouagadougou (HOSCO), Clinique Princesse Sarah (CPS) and CERBA. Patients' sociodemographic data, such as sex, age and place of residence, were recorded by the collection forms.

A case was defined as any patient presenting with at least two clinical signs suggestive of dengue with a positive RDT for DENV and confirmed by ELISA and presenting at least two signs suggestive of dengue fever, while controls were RDT- and ELISA-negative for DENV and presented no signs associated with dengue fever. Patients with an already well-known pathology were not included in this study.

Sampling mode

Sampling consisted of interviewing patients on a collection sheet. A blood sample was then taken from each study participant and distributed in two tubes: a dry tube and an EDTA tube. The collected samples were centrifuged at 4,000 G for 5 min, and then the plasma was used for the Rapid Diagnostic Test (RDT) for DENV. Sera from samples negative for Ag NS1 in the DENV RDT and control cases were tested by ELISA before being collected in Cryotubes and stored at -20°C.

Genomic DNA extractions

Genomic DNA was extracted using the rapid salting-out technique based on cell lysis, protein digestion and precipitation, impurity washing and DNA elution (10).

Amplification of DNA extracts by conventional PCR

For the detection of HLA-DRB1*11 and HLA-DRB1*12 by PCR, primers described by Ma et al. (11)were used with slight modifications. To ensure PCR reliability, a primer pair for amplification of the human growth factor (HGF) gene was also included as an internal control. This made it possible to confirm the presence of DNA in samples where none of the alleles studied were detected.

The technique involves multiplex PCR where the target alleles and the HGF internal control are amplified at the same time. This is performed with the GeneAmp PCR System 9700 (Applied Biosystems, USA) using a reaction volume of 25 µL. The reaction mixture consisted of 13 µL of molecular biology water, 4 µL of 5X master mix, 0.5 µL of each primer pair at a concentration of 0.2 µM, and finally the addition of 5 µL of DNA extract at 10 ng/µL per reaction.

The sequences of the primer pairs used are listed in Table 1.

Table 1. Primers and amplicon size

Genes	Primers	Amplicon size (bp)
DRB1*11	F : 5'GTTTCTTGGAGTACTCTACGTC3' R : 5'CTGGCTGTTCCAGTACTCCT3'	176
DRB1*12	F : 5'ACTCTACGGGTGAGTGTT3' R : 5'ACTGTGAAGCTCTCCACAG3'	244

HGF	F : 5'CAGTGCCTTCCCAACCATTCCCTTA3' R :5'ATCCACTCACGGATTTCTGTTGTGTTTC3'	432

PCR program

For amplification, the PCR program used consisted of an initial denaturation of the DNA for 10 minutes at 94°C, followed by 35 cycles, each consisting of a denaturation step at 94°C for 1 minute, a hybridization step at 56°C for 1 minute and finally an elongation step at 72°C for 1 minute. A final extension was performed at 72°C for 7 minutes.

Electrophoresis and revelation of PCR products

A 1X Tris Acetate EDTA (TAE) buffer was used to migrate PCR products by electrophoresis under non-denaturing conditions in a 2% agarose gel.

Validation of PCR product results

The PCR of a sample is validated if a band of amplification of the HGF gene is visible at the development stage. The PCR of a sample is invalid if the HGF gene amplification control band is not observed. The presence or absence of HLA DRB1*11 and HLA DRB1*12 alleles is linked to whether bands of the expected size are observed, namely, 176 bp for HLA DRB1*11 and 244 bp for HLA DRB1*12 (Figure 1).

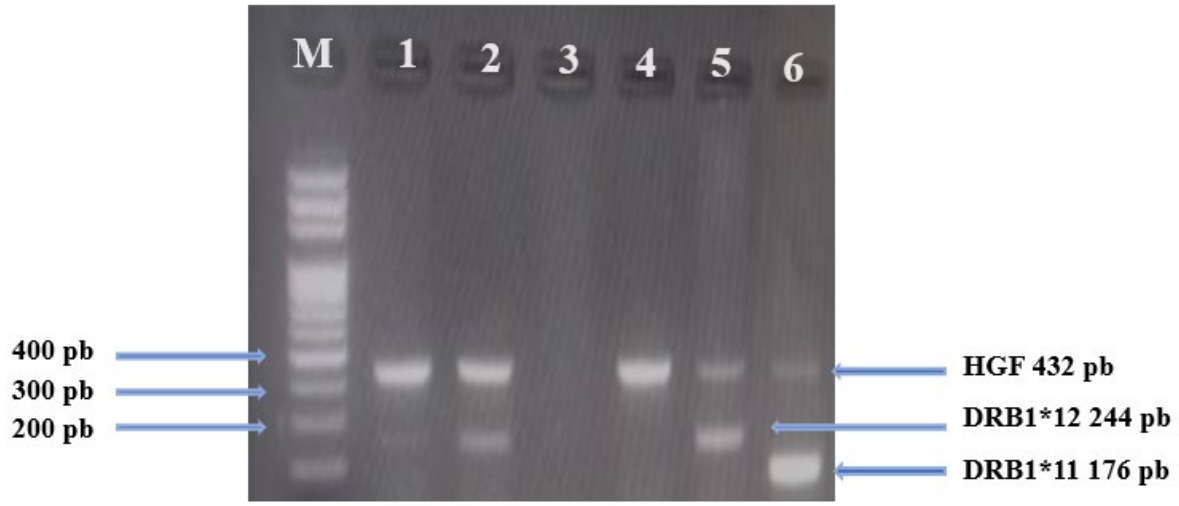

Figure 1. Electrophoresis gel of PCR products

M: *Molecular weight marker.* ***(1,2 and 5):*** *Presence of HLA-DRB1*12;* ***(3):*** *Invalid* ***(4):*** *Absence of HLA-DRB1*11 & HLA-DRB1*12* ***(6):*** *Presence of HLA-DRB1*11*

Data processing and analysis

Data were entered using Excel 2016 and then analyzed using R version 1.4.1717 and SPSS version 20. The chi-square test was used to compare frequencies. Odds ratios and 95% confidence intervals were calculated to assess risk. The results were considered statistically significant at $p < 0.05$.

Ethical considerations

This study was approved by the Ethics Committee for Health Research **CERS N° 25 48 89 37**. Written informed consent was obtained from patients and donors. We ensured the confidentiality of our database by storing it on a password-protected computer.

Results

Sociodemographic characteristics of the study population

This study involved 56 people with clinical signs of dengue confirmed by diagnostic tests in the medical biology laboratory and 65 people who had never been in contact with DENV, giving a total of 121 people. In our study population, 47.9% (58/121) were men, and 52.1% (63/121) were women, with a sex ratio of 0.67. Among DENV patients, half (28/56) or 23.1% were men (Table 2).

The most represented age group was between 16 and 30 years, i.e., 38.0%. This age group also had the highest incidence of dengue fever (18.2%). In our study population, the youngest was 2 years old, and the oldest was 75 (Table 2).

Table 2. Sociodemographic characteristics of the study population

Variables	Cases n (%)	Control n (%)	Total n (%)	P value
Gender				
Male	28 (23.1)	30 (24.8)	58 (47.9)	0.673
Female	28 (23.1)	35 (29.0)	63 (52.1)	
Age (years)				
0-15	6 (5.0)	15 (1.4)	21 (17.4)	0.115
16-30	22 (18.2)	24 (19.8)	46 (38.0)	
31-40	16 (13.2)	18 (14.9)	34 (28.1)	
41-60	8 (6.6)	8 (6.6)	16 (13.2)	
> 60	4 (3.3)	0 (0.0)	4 (3.3)	
Total	56 (46.3)	65 (53.7)	121 (100.0)	

n = numbers, % = frequencies

Virological and serological characteristics of patients

Data on serological and virological parameters are summarized in Table IV. The search for specific IgM and IgG antibodies tells us that in the study population, among the positive cases, 14.3% (8/56) had a primary infection with the DENV virus, (7/56) 12.5% had at least one previous infection and (26/56) 46.4% were in the secondary infection phase with another type of DENV or the recovery phase (Table 3).

Table 3. Prevalence of Ag NS1, IgG and IgM type Ac in the study population

	Cases	Control	Total
	n (%)	n (%)	n (%)
AgNS1	18 (32.14)	0 (0.0)	18 (100.0)
Ac-IgM-/IgG-	0 (0.0)	56 (100.0)	56 (100.0)
Ac-IgM-/IgG+	26 (46.4)	0 (0.0)	26 (100.0)
Ac-IgM+/IgG-	8 (14.3)	0 (0.0)	8 (100.0)
Ac-IgM+/IgG+	7 (12.5)	0 (0.0)	7 (100.0)

n: effectifs, **%**: sequences, **Ag**: antigen, **Ac**: antibodies, **NS1**: nonstructural protein 1
IgM -: Immunoglobulin M negative, **IgM +**: Immunoglobulin M positive, **IgG -**: Immunoglobulin G negative, **IgG +**: Immunoglobulin G positive.

Categorization of dengue cases in the study population

Table 4 shows the frequency of severe dengue cases among patients. Analysis of this table shows that 21.4% of patients developed the severe form of the disease. That is a total of 12/56. Men were the most affected, with a percentage of 12.5% (7/12), compared with 8.9% (5/12) for female patients.

Table 4. Categorization of dengue cases in the study population

Variables	Females n (%)	Males n (%)	Total n (%)	P value
DF	23 **(**41.1**)**	21 (37.5)	44 (78.6)	0.515
DS	5 (8.9)	7 (12.5)	12 (21.4)	
Total	28 (50.0)	28 (50.0)	56 (100.0)	

n: effectiveness, %: frequency, DS: severe dengue, DF: dengue fever

Frequency of HLA DRB1*11, HLA DRB1*12 alleles and their involvement in dengue infection.

In our population, the most frequent allele was DRB1*11 with a frequency of 64.4% and the DRB1*12 allele was 62.8%. No risk was found for separate carriage of the DRB1*11 and DRB1*12 alleles (OR = 0.65; 95% CI [0.30-1.39]; and p = 0.27) and the occurrence of dengue fever. However, for combinations of carriers of these two alleles, the absence of the HLA-DRB1*11 allele showed a protective effect against infection by the dengue virus (OR = 0.03; 95% CI [0.11 - 0.80]; and p = 0.01) (Table 5).

Table 5. Frequency of HLA DRB1*11 and HLA DRB1*12 alleles and their involvement in dengue infection

HLA Variables	Cases n %	controls n %	OR 95% CI	P value
DRB1* 11				
Present	39 (32.2)	39 (32.2)		Ref.
Absent	17 (14.0)	26 (21.5)	0.65 (0.30 - 1.39)	0.27

DRB1* 12				
Present	35 (28.9)	41 (33.9)		Ref.
Absent	21 (17.4)	24 (19.8)	1.02 (0.48 – 2.14)	0,948
DRB1*11 & 1*12				
DRB1*11+ & 1*12+	26 (21.4)	19 (15.7)	-	Ref.
DRB1*11+ & 1*12−	13 (10.7)	20 (16.5)	0.47 (0.19 – 1.18)	0.11
DRB1*11− & 1*12+	**9 (7.4)**	**22 (18.1)**	**0.03 (0.11 – 0.80)**	**0.01**
DRB 1*11− & 1*12−	8 (6.6)	4 (3.3)	1.46 (0.38-5.57)	0.58

n: effective, **%**: frequencies, OR 95% CI: odds ratio and 95% confidence interval

Frequency of HLA DRB1*11 and HLA DRB1*12 alleles and their involvement in recent dengue infection

From the analysis in Table 6, none of the DRB1*11 and 1*12 alleles were associated with DF in patients with primary DENV infection. This was observed both for separate carriage and for co-carriage of these two alleles.

Table 6. Frequency of HLA DRB1*11 and HLA DRB1*12 alleles and their involvement in recent dengue infection

HLA Variables	AgNs1+/IgM-/IgG- n %	Controls n %	OR 95% CI	P value
DRB1* 11				
Présent	11 (61,1)	39 (60,0)		Ref.
Absent	7 (38,9)	26 (40,0)	0.95 (0.33-2.78)	0.93
DRB1* 12				
Présent	9 (50,0)	41(63,0)		Ref.
Absent	9 (50,0)	24 (37,0)	1.71(0.53-4.90)	0.32
DRB1*11 & 1*12				
DRB1*11+ &1*12+	7 (38,9)	19 (29,2)		Ref.
DRB1*11+ & 1*12−	4 (22,2)	20 (30,7)	0.55 (0.14-2.16)	0.38
DRB1*11− & 1*12+	2 (11,1)	22 (33,9)	0.25 (0.05-1.33)	0.09
DRB 1*11− & 1*12−	5 (27,8)	4 (6,1)	3.39 (0.7016.38)	0.12

***n**: effects, %: frequencies, OR 95% CI: odds ratio and 95% confidence interval,* **NS1 +**: nonstructural protein 1 antigen test positive, **IgM -**: immunoglobulin M negative, **IgM +**: immunoglobulin M positive

Frequency of HLA DRB1*11 and HLA DRB1*12 alleles and their involvement in severe forms of dengue infection

With regard to the frequencies of these two alleles, we found no increase in the risk of developing severe dengue fever in carriers of the DRB1*11 and DRB1*12 alleles, when considering the separate or combined carriage of these two alleles (Table 7).

Table 7. Frequency of HLA DRB1*11 and HLA DRB1*12 alleles and their involvement in severe forms of dengue infection

HLA Variable	DF n %	DS n %	OR 95% CI	P value
DRB1* 11				
Present	30 (53.6)	9 (16.1)		Ref
Absent	14 (25.0)	3 (5.4)	1.40 (0.32 – 5.98)	0.650
DRB1* 12				

Present	26 (46.4)	9 (16.1)		Ref.
Absent	18 (32.1)	3 (5.4)	2.07 (0.49 – 8.75)	0.319
DRB1*11 & 1*12				
DRB1*11+ & 1*12+	19 (43.1)	7 (58.5)		Ref.
DRB1*11+ & 1*12−	11 (25.0)	2 (16.6)	2.02 (0.35-11.52)	0.42
DRB1*11− & 1*12+	7 (15.9)	2 (16.6)	1.29 (0.21-7.76)	0.78
DRB 1*11− & 1*12−	7 (15.9)	1 (8.3)	2.58 (0.27-24.90)	0.40

***n**: effectifs, %*: frequencies, DS: severe dengue. DF: Dengue Fever *OR 95% CI: Odds Ratio and 95% confidence interval*

Discussion

This study aimed to determine the involvement of HLA-DRB1*11 and HLA-DRB1*12 alleles in the occurrence of DENV infection and its progression to severe forms of the disease in Burkina Faso.

Dengue is a re-emerging viral disease almost worldwide, with seasonal frequencies in Burkina Faso.

According to our study, 14.3% (8/56) of patients were infected with DENV for the first time, while 85.7% (48/56) were infected for at least a second time or with a DENV serotype different from that of the previous infection. These results are similar to those of a study carried out in Burkina Faso in 2016, in which the secondary infection rate was 89.9%. (12). This high rate of secondary infection in our study population could be explained by the endemic nature of dengue fever in Burkina Faso.

According to gender, in our study, women were infected with dengue fever at the same rate as men, i.e., 23.1%. This result indicates that the disease affects both sexes almost equally. Our results are in line with those obtained in a study carried out in Burkina Faso, which estimated that women were slightly more infected than men, with no significant difference (5). The same is true of those obtained in a study carried out in Cuba on 120 individuals, including 54 women and 66 men. (13).

Our results show that 21.4% of the study population suffered from severe dengue fever. Of these. A total of 12.5% were men, and 8.9% were women. No significant difference was observed ($p = 0.515$). Severe dengue affects both men and women. However, in another study carried out in Vietnam, despite the low representation of men among dengue cases, female subjects had a higher risk of developing the severe form of the disease (14). This discrepancy between our results could be explained by our relatively small sample size and the almost equal representation of both sexes in our study population.

The HLA system is one of the most diverse genetic systems in humans. Our data indicated that the frequency of the HLA DRB1*11 allele was 64.4%, slightly higher than the frequency of the DRB1*12 allele (62.8%) in the general population. These results are similar to those obtained in a study carried out in Cuba, where the DRB1*11 allele was represented at 4.8% and the DRB1*12 allele at 0.5% (13). Similarly, another study of 318 descendants of black Africans in Brazil found that 13.05% had the DRB1*11 allele, while 1.72% had the DRB1*12 allele (15).

However, our results are not consistent with those obtained in the Tunisian population, where 49% of participants experiment with the DRB1*12 allele and only 14.36% experiment with DRB1*11 (16). The same is true for the results obtained in a population from Burkina Faso, where HLA DRB1*12 was the most represented, with a proportion of 56.63%, compared to 24.49% for HLA DRB1*11 (17).

This discrepancy between our results and those of other studies may be linked to the number of participants in each study. Most studies of both alleles report a higher frequency of the DRB1*11 allele (http://www.allelefrequencies.net/).

Various studies have investigated the possible association of HLA genes with the occurrence of dengue fever. Two alleles of the HLA DRB gene, namely: HLA-DRB1*11 and HLA-DRB1*12, are associated with protection against or susceptibility to dengue fever in different populations. In a study conducted in Mexico, the HLA-DRB1*11 allele was identified as a risk factor for the development of severe dengue fever. No association was found for the HLA-DRB1*12 allele (9). However, in another study conducted in Cuba, carriers of the HLA-DRB1*11 and HLA-DRB1*12 alleles did not present any risk of developing classic DF (18). Our results indicate that separate carriage of the DRB1*11 and DRB1*12 alleles is not associated with dengue risk.

These different studies therefore show different results depending on the population studied. Consequently, more in-depth studies in different populations are needed to establish meta-analyses that can be used for very detailed risk analyses.

Carrier combinations of these two alleles.

Deletion of the HLA-DRB1*11 allele was associated with a protective effect against the dengue virus (OR = 0.03; 95% CI [0.11 - 0.80]; and p = 0.01). Thus, a dengue sufferer with this mutated HLA DRB1 * 11 allele is less likely to develop a severe form of the disease.

To date, the pathophysiology of dengue fever is unclear. Evidence suggests that the disease is caused, at least in part, by an inappropriate immune response to the virus. The virus' dominant antigen (envelope protein E) is responsible for the entry of the virus into target cells and also induces protective immunity. This protein can also stimulate cross-reacting antibodies and CD4 and CD8 lymphocytes.

The antigenic determinants of the E protein can be processed and presented by MHC class II antigens. In this way, mutated HLA-DRB1*11 molecules can present these viral antigens to CD4 lymphocytes, generating an effective immune response and preventing dengue fever.

Conclusions

This study explored the frequency of HLA-DRB1*11 and DRB1*12 alleles and their involvement in the occurrence of dengue fever in Burkina Faso. The HLA-DRB1*11 allele was the most represented in the study population, with a frequency of 64.4%, compared with 62.6% for the DRB1*12 allele. No direct association between the carriage of these two alleles and the occurrence of dengue infection was proven. However, loss of the HLA-DRB1*11 allele was associated with protection against severe dengue fever.

In addition, further studies on other alleles of the HLA gene in large populations could provide additional information. If these results are corroborated, mutated HLA-DRB1*11 could indeed be an important genetic factor in resistance to DHF in Burkinabe populations.

Abbreviations list

ADN	**:**	Acide désoxyribonucléique
Ag NS1	:	Antigene Non-Structural Proteine
ARN	:	Acide ribonucléique
BET	:	Bromure d'éthidium
CERBA	:	Centre de Recherche Biomoléculaire Pietro Annigoni
CMH	:	Complexe majeur d'histocompatibilité
CPS	:	Clinique Princesse Sarah
DENV	:	Virus de la Dengue
DF	:	Dengue Fever ou fièvre dengue
DHF	:	Dengue Hémorragic Fever ou fièvre hémorragique dengue
DNTPs	:	Désoxynuléotides triphosphates (ATP, TTP, CTP, GTP)

DSS	:	Dengue Shock Syndrome
EDTA	:	Ethylene–Diamine–Tetra–Acetic acid
ELISA	:	Enzyme-Linked Immunosorbent Assay
GPI	:	Glycosyl-phosphatidyl-inositol
HGF	:	Human Growth Factor
HLA	:	Human Leucocyte Antigen
HOSCO	:	Hôpital Saint Camille de Ouagadougou
ICAM	:	Intracellular Adhesion Molecule
IFN	:	Interféron
KIR	:	Killer-immunoglobulin-like receptor
LAIR	:	Leucocyte-associated inhibitory receptor
MgCl2	:	Chlorure de magnesium
NK	:	Natural Killer
OMS	:	Organisation Mondiale de Santé
SPSS	:	Statistical Package for Social Sciences
TDR	:	Test de Diagnostic Rapide

Declarations

1. Ethics approval and consent to participate

This study was approved by the Ethics Committee for Health Research **CERS N° 25 48 89 37**. Written informed consent was obtained from patients and donors. We ensured the confidentiality of our database by storing it on a password-protected computer

2. Consent for publication

Not Applicable

3. Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

4. Competing interests

The authors declare that they have no competing interests.

5. Authors' contributions

Study concept and design: LT, OFK, BB, AMD, ATY, FWD and JS. Sampling and laboratory analysis: LT, OFK, ASAT, AKO, RK, MRY, FT, MS, NS, SOTB. Statistical analysis and data interpretation: LT, OFK, ASAT and AKO. Drafting of the manuscript: LT, OFK and ASAT. Critical revision of the manuscript for important intellectual content: RK, MRY, FT, MS, NS, SOTB BB, AMD, ATY, FWD and JS. Administrative, technical, and material support: LT, OFK, ASAT, AKO, FWD and JS. Study supervision: BB, AMD, ATY, FWD and JS. The corresponding author declares that the manuscript has been read and approved by all named authors and that the order of authorship in the manuscript has been approved by all of us.

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