The GC genotype of the MBL2 gene rs11003125 appears to be a protective factor indengue infection in Burkina Faso

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Abstract

Introduction: Dengue fever is a viral infection transmitted to humans by the bite of infected Aedes mosquito. Genetic factors in the human host play a role in the onset and progression of the disease's severe forms. The present study aimed to investigate the susceptibility to dengue fever according to MBL2 gene GC genotype in Ouagadougou, Burkina Faso. Method: A transversal study was conducted from September 2022 to May 2023, involving 110 peoples. Human genomic DNA was extracted using the Favorgen kit and *MBL2* gene polymorphisms genotypes were performed by real-time PCR using QuantStudio5. Results were analyzed using IBM SPSS Statistics 25 and Epi Info7 software.

Results: The participants had a mean age of 29.19 years with a range from 3 to 75 years. The population was predominantly female (60.91%). The combination of the two polymorphisms yielded 13.64% GC/CC and 0.91% GC/GG in the study population. The relationship was highly significant for both rs11003125 genotypes (GG and GC), with Chi-square values of 7.17 and 3.99, and p-values of 0.007 and 0.046, respectively. Conclusion: Our study has shown that the GC genotype of the *MBL2* gene *rs11003125 rs11003125* could be a protective factor in dengue infection in Burkina Faso.

Key words: DENV, *rs11003125*, *rs7096206*, *MBL2* gene, Burkina Faso.

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Introduction

Dengue is an arboviral disease, one of the infectious diseases of greatest concern to health authorities in the world's tropical and subtropical countries today, due to the increase in its incidence over the last fifteen years (1). It is a viral infection transmitted tohumans by the bites of infected *Aedes* mosquitoes. It can be febrile, acute, or mild, which constitutes dengue fever (DF), or severe and potentially fatal, which is dengue hemorrhagic fever (DHF). The causal agent is the dengue virus (DENV). It is an enveloped positive-sense RNA virus of the *Flaviviridae* family (2). Unlike other flaviviruses, it comprises four distinct serotypes (DENV1-4) (3).

Dengue is endemic in tropical and subtropical regions of the world (4). According to modeling estimates, 390 million dengue virus infections occur each year, of which 96 million manifest clinically (5). Exposure to dengue virus (DENV) provokes a variety of genetically controlled immunological responses. These include activation of dendritic cells, T cells, B cells and Natural Killers, as well as platelet destruction and production of antibodies and a range of cytokines, which together can be either protective or detrimental to people exposed to DENV (6). This counterpart the *MBL2* gene encodes a pathogen-recognition model molecule, mannose-binding lectin (MBL), which plays an essential role in virus elimination by enhancing phagocytosis and enabling activation of the complement system (7). Polymorphisms in the *MBL2* gene could influence the progression of dengue fever. Polymorphisms in the mannose-binding lectin (MBL2) gene affect the concentration and functional efficiency of the protein. Mannose-binding lectin (MBL) deficiency has been classified as a common immune disorder, affecting around 30% of the human population (8). The clinical impact of MBL deficiency and its association with a wide variety of diseases have been widely studied. It has been argued that the genetic heterogeneity of molecules involved in the host immune response to DENV infection, notably MBL, plays an important role in the development of severe disease. By focusing on the MBL2 gene located on chromosome 10 and encoding the mannose-binding lectin (MBL) protein, we investigated the involvement of the rs11003125 and rs7096206 polymorphisms in the susceptibility to develop severe forms of dengue fever in Burkina Faso. Previous studies have reported the involvement of the MBL2 gene in the infection and evolution of dengue fever (9,10) and most were focused on structural variants at

codons 52 (Arg/Cys) or allele D, 54 (Gly/Asp) or allele B and 57 (Gly/Glu) or allele C, as well as variants at the promoter region at -550 (alleles L/H), -221 (Y/X) and +4 (alleles P/Q)
Several studies on dengue fever in Burkina Faso have looked at the epidemiological aspects, the occurrence and forms of the disease, the vector, ecological and climatic factors and some genes, notably the KIR genes (1,11,12). However, no study has been carried out in the Burkinabe population to elucidate the role of *MBL2* gene polymorphisms in dengue fever susceptibility. Our study focused on the *rs11003125* and *rs7096206* polymorphisms of the *MBL2 gene*. We therefore set out to investigate the involvement of the *rs11003125* and *rs7096206* polymorphisms of the *MBL2* gene in the occurrence of dengue fever in Burkina Faso.

I. Materials and methods

I.1. Study Setting

The study occurred in the central health region of Ouagadougou, the capital of Burkina Faso. This region is in the Sudano-Sahelian zone, with an average annual temperature of 28°C and a rainfall of 788 mm. It lies between the Sahelian climate zone to the north and the Sudano-Guinean climate zone to the south, providing ideal conditions for the proliferation of Aedes mosquitoes, mainly Aedes aegypti and Aedes albopictus, the vectors of dengue fever. According to Ouedraogo et al. (2023), this region covers an area of 2857 square kilometers, with 3,032,668 inhabitants reported in 2019, and 70% of the total cases of dengue fever in the country are reported in this region (12).

I.2. Type and study period

This is a case-control study that was conducted from September 2022 to May 2023.

I.3. Study population

A total of 110 patients (51 cases and 59 controls) were included in the study. All patients seen for consultation during the sample collection period with at least two suggestive signs of dengue (fever, headache, etc.) without age limitation. The patients who were positive for NS1 antigens to the dengue rapid diagnostic test were included as dengue cases. Patients with no signs of dengue and tested negative for NS1 antigens were considered as control.

I.4. Sample collection and RDT processing

Samples were collected at four sites: Nongr Maasom Health District, Bogodogo Health District, Boulmiougou Health District and Baskuy Health District. EDTA (Ethylene-Diamine- Tetra-Acetic) blood sampling was carried out on positive patients using the Standard Dengue duo rapid detection kit. This product performs qualitative analysis on NS1 antigens of Dengue virus and Dengue virus-specific IgM/IgG in serum, plasma and whole blood.

I.5. Genotyping

DNA extraction and quantification: Participants' genomic DNAs were extracted from pellets using the Favorgen kit according to the manufacturer's protocol and quantification was performed using the Biodrop spectrophotometer (Cambridge, UK).

Genotyping of the *rs11003125* and *rs7096206* polymorphisms of the *MBL2* gene was carried out by real-time PCR using TaqMan® probes, the principle of which is based on the 5'exonuclease activity of DNA polymerase. For this purpose, the *Applied Biosystems™ TaqMan® MGB Probes* kit was used. Each genotyping reaction (25 µL total volume) consisted of 17.5 µL of distilled water, 3 µL of HOT FIREPol® Probe Universal qPCR Mix (5X concentration), 1.5 µL of TaqMan® SNP Genotyping Assays (diluted 1:5), and 3 µL of genomic DNA. The PCR conditions entailed an initial 10-minute denaturation step at 95°C, followed by 40 cycles: 15 seconds of denaturation at 95°C, 1-minute hybridization/extension at 60°C, and a concluding 30-second extension at 60°C. The specific primers employed for amplification.

I.6. Statistical analysis

Data were entered using Excel 2016. They were analyzed using IBM SPSS Statistics V25, Sphinx plus² V5 and Epi Info version 7. The chi-square test was used for frequency comparisons. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess risk. Results are considered statistically significant for a *p-value* of less than 0.05.

I.7. Ethical considerations

Subjects recruited were those who consented to participate in the study and gave their free and informed consent for blood sampling. The research protocol was approved by the Burkina Faso Health Research Ethics Committee (CERS) (CERS 2022-12-257). As for

the minors, asthey could not make decisions on their own, we had recourse to their parents or guardians and a witness, who was initially informed of the study's objectives and given the freedom to have their child participate in it.

II.1. Socio-demographic characteristics

A total of 110 patients were included in this study. The repartition of patients were 51 positive cases, and 59 negative controls (Table I). Analysis of Table I shows that 39.09% (43/110) of patients were male and 60.91% (67/110) female, with a sex ratio of 0.64. Among DENV-positive patients, 46.36% (51/110) were males (45.10%) versus 28 females (54.90%). In our study population, the mean age was 29.19 ± 11.56 years in the general population, 30.43 ± 12.62 years for patients, and 28.35 ± 10.31 years for controls. The 20-40 age group was the most represented, accounting for 66.36% of the population. This age group also had the highest incidence of dengue fever, at 56.86%.

Table I: Socio-demographic characteristics

	Cases N (%)	**Controls** N (%)	**Total** N (%)	***P-value***
Type				
Female	28 (54,90)	39 (66,10)	67 (60,91)	
Male	23 (45,10)	20 (33,90)	43 (39,09)	0,32
Total	51 (100)	59 (100)	110 (100)	
Age (years)				
< 20	10 (19,61)	9 (15,25)	19 (17,27)	
From 20 to 40	29 (56,86)	44 (74,58)	73 (66,36)	0,035
From 41 to 60	11 (21,57)	5 (8,48)	16 (14,55)	
> 60	1 (1,96)	1 (1,69)	2 (1,82)	
Total	51 (100)	59 (100)	110 (100)	

II.2. Distribution of RDT-positive cases by collection site

The distribution of patients by collection site shows that most cases were recorded in the Nongr Maasom Health District, with a percentage of 60.78% (Figure 1).

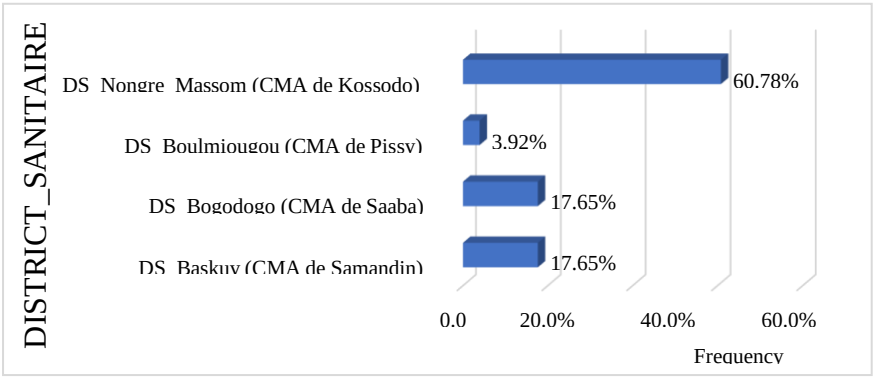

Figure 1: Distribution of positive cases by collection site.

II.3. Genotypic and allelic frequencies of rs11003125 (H/L) and rs7096206 (X/Y) of the MBL2 gene and their association with dengue.

Genotypic and allelic frequencies of *rs11003125 in* cases and controls were distributed as follows (Table II): The homozygous wild-type GG genotype accounted for 40.91% of the study population and 45.76% in the controls, compared with 35.29% in the cases. The distribution of GC heterozygotes was 59.09% in the study population, 54.24% and 64.71% in controls and cases respectively.

The homozygous mutated CC genotype was not observed in our study population, in either cases or controls. The frequencies of the G and C alleles were 70.90% and 29.10% in the study population, and 68.63% and 31.37% in patients, compared with 72.88% and 27.12% in negative controls. Genotypic and allelic frequencies of *rs7096206 in* cases and controls were distributed as follows (Table II): The homozygous wild-type CC genotype accounted for 36.36% of the study population and 37.29% in the controls, compared with 35.29% in the cases.

The distribution of CG heterozygotes was 62.73% in the study population, 62.71%, and 62.75% in controls and cases respectively.

The homozygous mutated GG genotype was only observed in 1.96% of positive cases. The frequencies of the C and G alleles were 68.18% and 31.82% in the study population, 66.67% and 33.33% in the patients and 69.49% and 30.51% in the negative controls.

Table II: Allelic and genotypic frequencies of MBL2 gene rs11003125 and *rs7096206* andtheir association with dengue.

	Cases	Controls		
	N= 51 (%)	**N= 59 (%)**	**OR (95% CI)**	***p-value***
rs11003125				
Genotypes				
GG (HH)	18 (35,29)	27 (45,76)	Ref	
GC (HL)	33 (64,71)	32 (54,24)	0,646 (0,299-1,395)	0,265
CC (LL)	0 (0,00)	0 (0,00)		
Alleles				
G (H)	35 (68,63)	43 (72,88)	Ref	
C (L)	16 (31,37)	16 (27,12)	0,814 (0,357-1,856)	0,624
rs7096206				
Genotypes				
CC (XX)	18 (35,29)	22 (37,29)	Ref	
CG (XY)	32 (62,75)	37 (62,71)	0,946 (0,433-2,068)	0,889
GG (YY)	1 (1,96)	0 (0,00)	-	
Alleles				
C (X)	34 (66,67)	41 (69,49)	Ref	
G (Y)	17 (33,33)	18 (30,51)	0,878 (0,393-1,1961)	0,751

OR: Odd Ratio; 95% CI: 95% Confidence Interval; Réf: reference

II.4. Analysis of combined genotypes in the general population and their association with dengue fever

Analysis of Table IV shows that in our population, after genotypic combination of *rs11003125 (HL)* and *rs7096206 (XY)*, we obtain 52.95% GC/CG (HL/XY) genotype, 25.5% GG/CC (HH/XX), 9,80% of GG/CG (HH/XY) and GC/CC (HL/XX) genotypes and 1.96% of GC/GG (HL/YY) in positive cases, versus 37.3% of GC/CG (HL/XY) genotype, 20.3% of GG/CC (HH/XX), 25.4% of GG/CG (HH/XY) genotypes, 16.9% of GC/CC (HL/XX) and 00% of GC/GG (HL/YY) in controls. The relationship is highly significant for both genotypesof rs11003125 (GG and GC), with Chi2 values of 7.17 and 3.99 respectively, and *p-values* of 0.007 and 0.046.

Table II Analysis of combined genotypes in the general population and their association withdengue.

		Rs11003125			
		Genotype			
		GG(HH)		GC(HL)	
		Cases (%)	Control (%)	Cases (%)	Control (%)
Rs7096206	CC(XX)	GG/CC (25.6)	GG/CC (20.3)	GC/CC (9.8)	GC/CC (16.9)
	CG(XY)	GG/CG (9.8)	GG/CG (25.5)	GC/CG (52.9)	GC/CG (37.3)
	GG(YY)	GG/GG (0,0)	GG/GG (0,0)	GC/GG (1.9)	GC/GG (0,0)
Chi2		7,17		3,99	
p-value		0,007		0,046	

II. Discussion

Our study consisted of determining and evaluating the genotypic and allelic frequencies, and the association of the *rs11003125* and *rs7096206* polymorphisms of the *MBL2* gene in the occurrence and evolution of DENV infection in the Burkinabè population.

Data analysis by socio-demographic characteristics covered a total of 110 participants, divided into 51 (46%) DENV-positive cases and 59 (54%) DENV-negative controls with 54.90% of women versus 45.10% of men. Our results were similar to those found by ILBOUDO *et al.* in 2022 in Burkina Faso (13) and those found by HIEN *et al.* in 2021 in Burkina Faso (14). These results could be explained by the high representation of women in the general population and their regular attendance at health centers. No significant statistical difference was found between gender and the occurrence of dengue fever. This result indicates that the disease affects both sexes almost equally. This is not in line with a study carried out in India with a sex ratio of 2 (15).

The two polymorphisms (*rs11003125* and *rs7096206*) in the *MBL2* gene were characterizedin the present study. In our study population, we identified the presence of *MBL2* polymorphisms and determined their frequency in both dengue cases and controls.

The homozygous wild-type GG, GC, and homozygous mutated CC genotype frequencies of the *rs11003125* polymorphism were 40.91%, 59.09% and 00% respectively in the study population and 35.29%, 64.71% and 00% in positive cases versus 45.76%, 54.24%

and 00% in controls. The CC genotype was not observed in our study. The frequency of G and C alleles was 70.90% and 29.10% respectively in the study population, and 68.63% and 31.37% in patients, versus 72.88% and 27.12% in negative controls. These results differ from those of Giang *et al.* in 2020, who found 26.4% for the homozygous mutated CC, 47.3% for the heterozygous GC, 26.4% for the homozygous wild GG and an allelic frequency of 50% G and50% C for the positive cases versus 23.5% CC, 44.7% GC and 31.8% GG and an allelic frequency of 45.9% C and 54.1% G for the control cases. (18). Our results alsodiffer from those of Sena *et al*, in 2022 who found 54.0% of homozygous mutated CC, 33.0% of heterozygous GC, 13.0% of homozygous wild GG for positive cases versus 53.2% of homozygous mutated CC, 37.7% of heterozygous GC and 9.1% of homozygous wild GG and an allelic frequency of 28.0% of allele G and 72.0% of allele C for controls (19). The association of *MBL2* gene polymorphisms with DENV infections has been documented, in particular promoter polymorphisms (-550,-221 and +4) were correlated with low MBL levels and were associated (18). In our study, the associations of the *rs11003125* polymorphism with the occurrence of dengue fever were not statistically significant, as the odds ratio was OR = 0.646; 95% CI = 0.299-1.395. This association does not indicate protection against disease occurrence in the presence of the GG genotype, as the p-value was greater than 0.05 ($p = 0.265$).

The genotypic frequencies of wild-type homozygous CC, heterozygous CG and mutated homozygous GG of the *rs7096206* polymorphism were 36.36%, 62.73% and 0.91% respectively in the study population, and 35.29%, 62.75% and 1.96% in positive cases versus 37.29%, 62.71% and 00% in controls. The homozygous mutated GG genotype was observed only in the population of positive cases, at 1.96%. The frequency of C and G alleles was 68.18% and 31.82% respectively in the study population, and 66.67% and 33.33% in the patients, compared with 69.49% and 30.51% in the negative controls. These results differ from those of Giang *et al.* in 2020, who found 8.6% of the homozygous mutated GG, 39.0% of the heterozygous CG, and 52.4% of the homozygous wild-type CC in the positive cases. On the other hand, allele frequencies were virtually identical: 71.9% for the C allele and 28.1% for the G allele in positive cases, versus 74.9% for the C allele and 25.1% for the G allele in control cases (18). Our results also differ from those of Sena *et al.* in 2022, who found more mutated homozygotes, i.e. 51.1% GG,

44.5% CG heterozygote and 4.4% CC wild-type homozygote for positive cases, versus 73.8% GG mutated homozygote, 23.7% CG heterozygote and 2.5% CC wild-type homozygote for control cases. And regarding the allelic frequency of C and G, our results are inconsistent, with 73.3% for the G allele and 26.7% for the C allele for the control cases (19). There was no association between the *rs7096206* polymorphism of the *MBL2* gene and the occurrence of dengue fever, as the odds ratio OR = 0.946; 95% CI = 0.433-2.068. This means that it does not protect against the onset of the disease, as the *p-value* was greater than 0.05 (p = 0.889).

Analysis of the genotype and allele frequencies of the study population showed that the various genotypes and alleles in the sample were in Hardy Weinberg equilibrium.

This is true for both cases and controls (P > 0.05) for the two polymorphisms *rs11003125* and *rs7096206*, respectively ($p = 0.094$ of cases and $p = 0.185$ of controls and $p = 0.166$ of cases and $p = 0.098$ of controls). Indeed, Hardy Weinberg's law states that within a population, allelic and genotypic frequencies remain constant from one generation to the next. This meansthat these polymorphisms will be constant from one generation to the next.

To evaluate or highlight the combined effect of polymorphisms on the risk of dengue occurrence, we were only able to combine two polymorphisms of the *MBL2* gene promoter, namely *rs11003125* and *rs7096206*. This combination enabled us to obtain 22.73% of the normal GG/CC genotype, 44.54% of the GC/CG genotype, 18.18% of GG/CG, 13.64% of GC/CC and 0.91% of GC/GG in the study population, and 52.95% of the GC/CG genotype, 25.5% of GG/CC, 9.80% of GG/CG and GC/CC genotypes and 1.96% of GC/GG in positive cases, versus 37.3% of GC/CG genotype, 20.3% of GG/CC, 25.4% of GG/CG genotypes, 16.9% of GC/CC and 0.0% of GC/GG in controls. Most studies on *MBL2* gene polymorphisms combine all six polymorphisms to determine the exact effect of *MBL2* gene polymorphisms in DENV infections, as well as the association of the MBL protein with the organism's susceptibility or protection against DENV. Genotype analysis of individual polymorphisms was statistically insignificant. In other words, there was no relationship between each polymorphism and the occurrence of severe forms of dengue fever. But after combination, there was a relationship between the combination and the occurrence of dengue severity. We believe that the effects of a single polymorphism are often negligible in causing the occurrence of any form of dengue, suggesting that

polymorphisms act synergistically to provide either protection or susceptibility.

The limitations of our study lie mainly in the determination of the other polymorphisms of the *MBL2 gene* and the MBL protein assay. We were unable to determine all six major polymorphisms of the *MBL2 gene.* We were also unable to assay MBL protein concentration to study the effect of polymorphisms on MBL protein concentration in DENV infection.

Conclusion

Our study is the first in Burkina Faso to investigate the probable links between the rs11003125 and rs7096206 polymorphisms of the *MBL2* gene in the occurrence of severe forms of dengue fever in Burkina Faso. Our study reports a mutant [C] allele frequency for *rs11003125* of 29.10% in the study population, 32% in cases and 27% in controls. And for *rs7096206*, the mutant [G] allele had frequencies of 31.82% in the study population, 33% and 31% in cases and controls respectively. The combination of the two polymorphisms gave us 13.64% GC/CC and 0.91% GC/GG in the study population, 9.80% GC/CC and 1.96% GC/GG in positive cases, compared with 16.9% GC/CC and 00% GC/GG in controls. From a genetic point of view, the [C] allele resulting from the mutation (GC and CC) of *rs11003125* was associated with a reduced risk of occurrence of severe forms of dengue fever. On the other hand, the [G] allele resulting from the mutation (CG and GG) of *rs7096206* was associated with an increased risk of severe forms of dengue fever.

Ethics approval and consent to participate

This study was approved by the Ethics Committee for Health Research N° CERS 2022-12-257. Written informed consent was obtained from patients and donors. We ensured theconfidentiality of our database by storing it on a password-protected computer

Consent for publication

Not Applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Study concept and design: LT, MT, TRC, JCRPO, FWD and JS. Sampling and laboratory analysis: LT, MT, MS, JCRPO, TCO, AMSAT, Statistical analysis and data interpretation: LT, MT, JCRPO and TCR. Drafting of the manuscript: LT, MT, MS, AMSAT and TCO. Critical revision of the manuscript for important intellectual content: TCR, WMCN, PDI, NS, ATY, FWD and JS. Administrative, technical, and material support: LT, JCRPO, FWD, WMCN, PDI and JS . Study supervision: FWD, WMCN, PDI 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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