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Clinical and Molecular Associations of Il-1β, Tnf-α, and Il-8 Polymorphisms in Dengue Patients

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Abstract

Background

Dengue is a major arboviral disease where polymorphisms in genes encoding inflammatory mediators may modulate the immune response to dengue virus (DENV) infection. Thus, this study aimed to investigate the association of *IL-1β* rs1143634, *IL-8* rs4073, and *TNF-α* rs361525 polymorphisms with susceptibility to DENV infection and with clinical manifestations and laboratory parameters.

Methods

A case-control study was conducted in Goiânia, Goiás, Brazil, including individuals with confirmed DENV infection. Genomic *IL-1β* rs1143634, *IL-8* rs4073, and *TNF-α* rs361525 polymorphisms were genotyped using TaqMan assays and real-time PCR. Logistic regression, Fisher's exact test, and Student's *t*-test were used for statistical analyses. Clinical and laboratory data were evaluated according to genotype.

Results

No significant association was observed between the evaluated polymorphisms and susceptibility to DENV infection ($p > 0.05$). Similarly, no significant association was observed between polymorphisms and the overall number of clinical symptoms. However, the *IL-8* rs4073 polymorphism was significantly associated with serum aminotransferase levels, AST ($p = 0.002$) and ALT ($p = 0.040$). The *TNF-α* rs361525 polymorphism was significantly associated with platelet count ($p < 0.001$). In addition, *IL-1β* rs1143634 was significantly associated with low back pain ($p = 0.040$).

Conclusion

The association between *IL-8* rs4073 and AST and ALT levels suggests a potential role of this polymorphism in hepatic involvement during dengue. Furthermore, the association of *TNF-α* rs361525 with thrombocytopenia and *IL-1β* rs1143634 with low back pain further supports the potential contribution of inflammatory genetic variants to the clinical heterogeneity of dengue. Larger studies are required for underlying biological mechanisms.

INTRODUCTION

Dengue is an arboviral disease with major global impact, caused by the dengue virus (DENV), a flavivirus transmitted primarily by mosquitoes of the genus *Aedes*, especially *Aedes aegypti* and *Aedes albopictus*. Infection may present asymptomatically or progress to different clinical manifestations, ranging from a self-limiting febrile illness to severe forms of the disease, characterized by shock, severe hemorrhage, and organ dysfunction [1].

Current evidence indicates that host genetic factors, including polymorphisms in genes involved in inflammatory and immune responses, have been investigated as potential modulators of susceptibility to DENV infection and disease severity [2]. Given the increasing global incidence and the challenges associated with vector control and effective immunization, dengue remains a major public health challenge; thus, understanding the immunological and genetic mechanisms involved in disease progression may contribute to the development of more effective prevention and treatment strategies [2, 3].

Therefore, the aim of this study was to understand the role of the single nucleotide polymorphisms (SNPs) *IL-1β* rs1143634, *IL-8* rs4073, and *TNF-α* rs361525 in the genetic susceptibility to dengue virus (DENV), and to identify the possible relationship between the presence of these SNPs and clinical symptoms.

MATERIALS AND METHODS

This is a case-control study involving individuals infected with DENV and control individuals without the disease. The study was approved by the Research Ethics Committee of the Pontifical Catholic University of Goiás (PUC-GO) under CAAE number 36430120.4.3001.8058 and followed all ethical principles of the Declaration of Helsinki. Sample collection was carried out in

Goiânia - GO, Brazil. Furthermore, participants of the study provided informed consent. All individuals were tested by immunofluorescence using the Eco Diagnostic LTDA kit for confirmation of the viral NS1 protein and IgM antibodies.

DNA was obtained from whole blood samples, buffy coats, or peripheral blood mononuclear cells (PBMCs); and the kit used was the PureLink Genomic DNA Mini Kit® (Invitrogen™, Thermo Fisher Scientific). For quantification, the NanoDrop Sctitek spectrophotometers (Thermo Scientific NanoDrop) were used.

TaqMan probes were used for human genotyping of the SNPs *IL-1β rs1143634* G > A (C_9546517_10), *IL-8 rs4073* A > T (C_11748116_10), and *TNF-α rs361525* G > A (C_2215707_10) (Thermo Fisher Scientific). Genotyping was performed in duplicate; and positive controls, blanks, and negative controls were used in all tests. Genotyping was performed using a real-time PCR thermal cycler (LightCycler® 480 II, Roche). Furthermore, complementary laboratory tests were done. Details of the protocol are described at protocols.io (https://dx.doi.org/10.17504/protocols.io.6qpvr9ow3vmk/v1; https://dx.doi.org/10.17504/protocols.io.5qpvowzrdl4o/v1; https://dx.doi.org/10.17504/protocols.io.bp2l68bxdgqe/v1).

Study analysis was statistically analyzed with R software version 4.3.2. Logistic regression analysis was performed to evaluate the association between genotypes under different genetic inheritance models. Allelic frequencies were also analyzed, as well as Hardy–Weinberg equilibrium test. Finally, the association between genotypes and clinical variables was evaluated using Student's *t*-test. Statistical significance was defined as $p < 0.05$.

RESULTS AND DISCUSSION

The study population consisted of 96 individuals for the *IL-1β* gene analysis, 93 and 82 individuals for *IL-8* and *TNF-α* gene analysis, respectively. The study population was evaluated for Hardy-Weinberg equilibrium, and overall, the *IL-1β* rs1143634 and *IL-8* rs4073 polymorphisms were found to be in equilibrium, suggesting that the study sample is representative of the analyzed population and that there is no evident sampling bias [4]. In contrast, the *TNF-α* rs361525 polymorphism showed evidence of Hardy–Weinberg disequilibrium in the case group ($p = 0.008$). This deviation is likely attributable to the low frequency of individuals carrying the mutant AA genotype.

According to Table 1, when interpreting the results for the *IL-1β* rs1143634 SNP *IL-8* rs4073, *TNF-alfa* rs361525 polymorphisms under the different genetic inheritance models, no significant association was found ($p > 0.05$). These findings suggest that the presence of these SNPs was not associated with increased susceptibility of dengue infection under the evaluated genetic models.

Table 1
Comparison of the genetic inheritance models for *IL-1β* rs1143634, *IL-8* rs4073, *TNF-alfa* rs361525 polymorphism and allelic association in dengue patients.

SNP	GENETIC MODEL	GENOTYPE	NO	YES	ODDS (CI 95%)	P-VALUE	AIC	BIC
IL-1β rs1143634	Codominant	G/G	46 (79.31%)	33(68.75%)	Ref	Ref	150.406	158.396
		G/A	10 (17.241%)	13(27.083%)	1.812(0.713–4.729)	0.214		
		A/A	2 (3.448%)	2(4.167%)	1.394(0.161–12.103)	0.746		
	Dominant	G/G	46 (79.31%)	33(68.75%)	Ref	Ref	148.464	153.791
		G/A + A/A	12 (20.69%)	15(31.25%)	1.742(0.724–4.271)	0.217		
	Recessive	G/G + G/A	56 (96.552%)	46(95.833%)	Ref	Ref	149.965	155.292
		A/A	2 (3.448%)	2(4.167%)	1.217(0.142–10.467)	0.847		
	Overdominant	G/G + A/A	48 (82.759%)	35(72.917%)	Ref	Ref	148.51	153.837
		G/A	10 (17.241%)	13(27.083%)	1.783(0.705–4.628)	0.224		
	Allele	G	102	79	-	0.336	-	-
		A	14	17	-	-	-	-
IL-8 rs4073	Codominant	A/A	17 (36.17%)	8(17.778%)	Ref	Ref	129.361	136.926
		A/T	19 (40.426%)	25(55.556%)	2.796(1.021–8.156)	0.051		
		T/T	11 (23.404%)	12(26.667%)	2.318(0.728–7.747)	0.16		
	Dominant	A/A	17 (36.17%)	8(17.778%)	Ref	Ref	127.493	132.536
		A/T + T/T	30 (63.83%)	37(82.222%)	2.621(1.02–7.208)	0.051		
	Recessive	A/A + A/T	36 (76.596%)	33(73.333%)	Ref	Ref	131.365	136.409
		T/T	11 (23.404%)	12(26.667%)	1.19(0.461–3.098)	0.718		
	Overdominant	A/A + T/T	28 (59.574%)	20(44.444%)	Ref	Ref	129.379	134.422
		A/T	19 (40.426%)	25(55.556%)	1.842(0.81–4.264)	0.148		
	Allele	A	53	41	-	0.186	-	-
		T	41	49	-	-	-	-
TNF-alfa rs361525	Codominant	G/G	33 (82.5%)	40(93.023%)	Ref	Ref	116.062	123.318

SNP	GENETIC MODEL	GENOTYPE	NO	YES	ODDS (CI 95%)	P-VALUE	AIC	BIC
		G/A	7 (17.5%)	2(4.651%)	0.236(0.034–1.053)	0.084		
		A/A	0(0%)	1(2.326%)	4750195.61(0-NA)	0.992		
	Dominant	G/G	33 (82.5%)	40(93.023%)	Ref	Ref	116.745	121.582
		G/A + A/A	7 (17.5%)	3(6.977%)	0.354(0.072–1.38)	0.154		
	Recessive	G/G + G/A	40 (100%)	42(97.674%)	Ref	Ref	117.627	122.465
		A/A	0 (0%)	1(2.326%)	5483631.295(0-NA)	0.991		
	Overdominant	G/G + A/A	33 (82.5%)	41(95.349%)	Ref	Ref	115.254	120.092
		G/A	7 (17.5%)	2(4.651%)	0.23(0.033–1.027)	0.078		
	Allele	G	73	82	-	0.454	-	-
		A	7	4	-	-	-	-

Logistic regression was used to compare the genetic inheritance models, whereas allelic associations were assessed using Fisher's exact test. Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; CI = Confidence Interval 95%; OR = Odds Ratio; Ref: Reference genotype. Significance between groups: $p < 0.05$.

When *IL-1β* rs1143634 SNP was investigated in patients with intrahepatic cholangiocarcinoma, it was found a significant association between the SNP and a higher risk of death and, also with a higher risk of recurrence [5]. In a meta-analysis, this SNP was identified as a potential genetic biomarker of Hepatitis B virus (HBV) infection [6]. Furthermore, among individuals infected with HIV-1, the GA genotype was significantly associated with an increased risk of developing tuberculosis (aOR = 5.5; $p = 0.044$) [7].

On the other hand, the *IL-8 rs4073* SNP was not significantly associated with aggressive periodontitis, similarly to our results [8]. *TNF-α rs361525* polymorphism was not significantly associated with dengue infection either, which may be partly attributed to the low frequency of the mutant A/A genotype in our sample. Consistent with our findings, a meta-analysis investigating the association between dengue infection and the *TNF-α rs361525* polymorphism reported no significant association [9].

Furthermore, given the clinical relevance of the manifestations associated with dengue virus infection, an analysis was conducted to assess the association between different genotypes of the SNPs and the number of clinical symptoms exhibited by individuals infected with DENV (Table 2).

Table 2
Association between SNPs genotypes and the number of symptoms among dengue virus (DENV) infected individuals.

SNP	Genotype	≤ 6 Symptoms	6 e 11 Symptoms	> 11 Symptoms	p-value
IL-1β rs1143634	GG	10	15	8	0,761
	GA	3	5	5	
	AA	1	1	0	
IL-8 rs4073	AA	1	5	2	0,067
	AT	8	6	11	
	TT	3	8	1	
TNF-alfa rs361525	GG	11	18	11	0,516
	GA	1	1	0	
	AA	1	0	0	

Chi-square test. Statistical significance was $p < 0.05$.

In addition, an analysis was performed to evaluate the association of the *IL-1β* rs1143634, *IL-8* rs4073, and *TNF-α* rs361525 genotypes with laboratory and anthropometric variables. For each polymorphism, the genotypes were grouped into wild type versus heterozygous + mutant genotypes (Table 3).

Table 3
Association between genotypes and laboratory and anthropometric variables.

SNP	Genotype	Average	SD	Variable	*p* value
IL-1β rs1143634	G/G	8,364	3,647	Number of symptoms	0,378
	G/A + A/A	9,333	3,395		
	G/G	4,611	0,456	Red blood cells	0,112
	G/A + A/A	5,003	0,816		
	G/G	40,755	4,194	Hemoglobin	0,101
	G/A + A/A	43,607	5,494		
	G/G	13,776	1,343	Hematocrit	0,138
	G/A + A/A	14,729	2,103		
	G/G	161106,897	61371,171	Platelets	0,218
	G/A + A/A	132021,429	74557,816		
	G/G	4805,517	2557,014	White blood cells	0,640
	G/A + A/A	5227,143	2814,999		
	G/G	57,517	47,276	Eosinophils	0,936
	G/A + A/A	58,929	56,023		
	G/G	1335,655	1002,225	Lymphocytes	0,393
	G/A + A/A	1080,857	852,825		
	G/G	410,793	226,855	Monocytes	0,284
	G/A + A/A	501,500	265,681		
	G/G	2681,006	10998,390	CRP mg/L	0,333
	G/A + A/A	18,486	19,481		
	G/G	71,462	15,938	Weight	0,120
	G/A + A/A	78,154	10,090		
	G/G	1,638	0,098	Height	0,335
	G/A + A/A	2,099	1,656		
	G/G	26,104	4,710	BMI	0,989
	G/A + A/A	26,139	8,129		
	G/G	74,143	74,766	AST u/l	0,643
	G/A + A/A	61,333	55,581		
	G/G	76,714	98,656	ALT u/l	0,492
	G/A + A/A	56,556	33,934		
IL-8 rs4073	AA	9,375	4,207	Number of symptoms	0,723
	AT + TT	8,789	3,670		

Student's t-test was used for statistical analysis. * Significant results ($p < 0.05$). Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CRP = C-reactive protein; SD = Standard deviation;

SNP	Genotype	Average	SD	Variable	*p* value
	AA	4,652	0,190	Red blood cells	0,890
	AT + TT	4,671	0,641		
	AA	41,100	1,835	Hemoglobin	0,584
	AT + TT	41,768	5,239		
	AA	13,733	0,455	Hematocrit	0,538
	AT + TT	13,965	1,790		
	AA	154233,333	46571,307	Platelets	0,654
	AT + TT	143838,710	66601,059		
	AA	4148,333	1890,147	White blood cells	0,695
	AT + TT	4498,387	2086,238		
	AA	66,000	85,762	Eosinophils	0,671
	AT + TT	49,968	37,762		
	AA	1036,333	835,652	Lymphocytes	0,684
	AT + TT	1199,161	1001,031		
	AA	334,833	99,807	Monocytes	0,091
	AT + TT	443,645	255,777		
	AA	32,133	27,363	CRP.mg/L	0,334
	AT + TT	2171,910	9895,870		
	AA	76,333	10,633	Weight	0,276
	AT + TT	69,935	19,967		
	AA	2,474	2,262	Height	0,367
	AT + TT	1,640	0,100		
	AA	24,198	11,761	BMI	0,816
	AT + TT	25,404	6,409		
	AA	17,500	2,121	AST u/l	**0,002***
	AT + TT	80,250	67,205		
	AA	26,000	15,556	ALT u/l	**0,040***
	AT + TT	82,875	88,837		
TNF-alfa rs361525	G/G	8,500	3,471	Number of symptoms	0,224
	G/A + A/A	5,667	2,887		
	G/G	4,776	0,662	Red blood cells	0,615
	G/A + A/A	5,165	0,799		
	G/G	42,153	5,185	Hemoglobin	0,855

Student's t-test was used for statistical analysis. * Significant results ($p < 0.05$). Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CRP = C-reactive protein; SD = Standard deviation;

SNP	Genotype	Average	SD	Variable	*p* value
	G/A + A/A	41,050	6,718		
	G/G	14,316	1,817	Hematocrit	0,771
	G/A + A/A	13,900	1,556		
	G/G	152284,375	60042,921	Platelets	**0,000***
	G/A + A/A	69500,000	9192,388		
	G/G	5058,750	2733,794	White blood cells	0,956
	G/A + A/A	5250,000	3889,087		
	G/G	58,000	50,106	Eosinophils	0,876
	G/A + A/A	52,500	38,891		
	G/G	1311,781	979,887	Lymphocytes	0,914
	G/A + A/A	1452,500	1453,104		
	G/G	474,781	256,310	Monocytes	0,964
	G/A + A/A	460,000	367,696		
	G/G	2850,094	11336,253	CRP mg/L	-
	G/A + A/A	-	-		
	G/G	73,500	14,774	Weight	-
	G/A + A/A	-			
	G/G	6,527	18,613	Height	-
	G/A + A/A	-	-		
	G/G	25,827	6,607	BMI	-
	G/A + A/A	-	-		
	G/G	64,547	66,225	AST u/l	-
	G/A + A/A	-	-		
	G/G	71,357	89,120	ALT u/l	-
	G/A + A/A	-	-		

Student's t-test was used for statistical analysis. * Significant results ($p < 0.05$). Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CRP = C-reactive protein; SD = Standard deviation;

Although previous studies have reported associations between genetic polymorphisms and specific clinical manifestations of dengue [10, 11], the present study found no significant association between the evaluated SNPs and the overall number of symptoms among DENV-infected individuals. When evaluated genotypes and laboratory and anthropometric variables, the analysis showed that *IL-1β* rs1143634 had no p-value < 0,05.

However, the *IL-8* rs4073 polymorphism was significantly associated with AST and ALT levels ($p = 0.002$ and $p = 0.040$, respectively), which are commonly used biochemical markers of hepatic involvement in dengue. Previous studies have demonstrated an important role of IL-8 in the inflammatory response in some diseases, including DENV infection, with significantly higher serum IL-8 levels observed in dengue patients compared with healthy controls [10–13]. Moreover, genetic variation in the *IL-8* gene has been investigated as a potential modulator of IL-8 production [5, 8, 12, 13]. Therefore, the association observed between *IL-8* rs4073 and aminotransferase levels in the present study may reflect differences in

inflammatory responses and hepatic involvement among DENV-infected individuals. Further studies are needed to elucidate the biological mechanisms underlying this association.

Finally, the *TNF-α* rs361525 polymorphism was significantly associated with platelet count ($p < 0.001$), suggesting a potential association between this genetic variant and thrombocytopenia in DENV-infected individuals. Thrombocytopenia is a common hematological abnormality in dengue and is closely associated with disease progression and severity [14]. In addition, increased TNF-α levels have been associated with reduced platelet counts in patients with dengue, supporting a potential role of this pro-inflammatory cytokine in dengue-associated thrombocytopenia [15]. Experimental evidence has further demonstrated that elevated TNF-α may contribute to platelet depletion through thrombophagocytosis by mononuclear cells during DENV infection [16]. Therefore, the association observed in the present study raises the possibility that the *TNF-α* rs361525 polymorphism may contribute to differences in platelet homeostasis during dengue. However, further studies are required to determine whether this polymorphism influences TNF-α expression or activity and to clarify the biological mechanisms underlying its association with platelet counts.

In addition, it was analyzed the association of individual clinical symptoms and polymorphisms (Table 4).

Table 4
Association between the most frequently reported symptoms among DENV-infected individuals and SNPs.

SYMPTOMS	***IL-1B* rs1143634**	***IL-8* rs4073**	***TNF-a* rs361525**
Previous dengue infection	0,285	0,392	0,693
Fever	0,593	0,642	0,961
Joint pain	0,424	0,660	0,530
Headache	0,473	0,566	0,684
Nausea	0,612	0,089	0,306
Diarrhea	0,364	0,931	0,263
Vomiting	0,669	0,862	0,230
Fatigue/Prostration	0,621	0,864	0,223
Muscle pain/Myalgia	0,088	0,778	0,093
Swelling/Edema	0,691	0,518	0,604
Enlarged lymph nodes	0,234	0,458	0,532
Red eyes/Conjunctival hyperemia	0,326	0,783	0,298
Low back pain	**0,040***	0,660	0,141
Pruritus	0,445	0,077	0,408
Rash	0,552	0,791	0,485
Ear pain	0,531	0,800	0,532
Eye pain/Retro-orbital pain	0,626	0,378	0,653

Chi-Square Test. * Significant results ($p < 0.05$).

Among the evaluated clinical manifestations, low back pain demonstrated a statistically significant association with the *IL-1β rs1143634* polymorphism ($p = 0.040$). *IL-1β* gene may be associated with the course and severity of pain. Previous studies have suggested that genetic variation in inflammatory mediators may contribute to specific clinical manifestations of dengue [10–12]. In Brazilian dengue patients, Cansanção et al. [10] reported an association between the *IL-1β* − 511C > T polymorphism (rs16944)

and dizziness, with T-allele carriers showing a higher frequency of this manifestation (OR = 8.18, $p = 0.01$). Similarly, in the present study, the *IL-1β* rs1143634 polymorphism was associated with low back pain ($p = 0.040$), suggesting that genetic variation within the *IL-1β* gene may contribute to differences in specific clinical manifestations among DENV-infected individuals.

CONCLUSION

In conclusion, the genomic analysis of the *IL-1β* rs1143634, *IL-8* rs4073, and *TNF-α* rs361525 polymorphisms in individuals infected with DENV enabled the identification of potential genetic associations between these polymorphisms and laboratory parameters, as well as in signs and symptoms in DENV Brazilian population patients. Despite the limitation imposed by the relatively small sample size, the findings provide new insights into the relationship between single nucleotide polymorphisms and the immune response during DENV infection, laying the groundwork for future research aimed at improving scientific knowledge, disease management and public health.

Abbreviations

AIC
Akaike Information Criterion
ALT
Alanine Aminotransferase
AST
Aspartate Aminotransferase
BIC
Bayesian Information Criterion
CAAE
Certificate of Presentation for Ethical Appreciation
CI
Confidence Interval
CNPq
National Council for Scientific and Technological Development
DENV
Dengue Virus
DNA
Deoxyribonucleic Acid
FAPEG
Research Support Foundation of the State of Goiás
HBV
Hepatitis B Virus
HIV-1
Human Immunodeficiency Virus Type 1
IL-1β
Interleukin-1 beta
IL-6
Interleukin-6
IL-8
Interleukin-8
IgM
Immunoglobulin M
NS1
Non-Structural Protein 1
OR

Odds Ratio
PBMCs
Peripheral Blood Mononuclear Cells
PCR
Polymerase Chain Reaction
PUC-GO
Pontifical Catholic University of Goiás
SD
Standard Deviation
SNP
Single Nucleotide Polymorphism
TNF-α
Tumor Necrosis Factor-alpha.

Declarations

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COMPETING INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

R.S.C: Methodology, Investigation, Data curation**,** Formal analysis, Writing – original draft, Writing – review and editing; **V.R.M.C.L:** Methodology, Investigation, Writing – review and editing; **L.P.A:** Formal analysis, Statistical analysis, Data interpretation, Writing – review and editing; **A.P.V.M.M, M.V. S, J.O.A.P, G.R.S:** Methodology, Investigation, Writing – review and editing; **J.B.S.B; I.A.H.P**: Conceptualization, Methodology, Investigation, Formal analysis, Supervision, Project administration, Funding acquisition, Writing – original draft, Writing – review and editing. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

RESEARCH INVOLVING HUMAN PARTICIPANTS, THEIR DATA OR BIOLOGICAL MATERIAL

The study was approved by the Research Ethics Committee of the Pontifical Catholic University of Goiás (PUC-GO) under CAAE number 36430120.4.3001.8058 and followed all ethical principles of the Declaration of Helsinki. Furthermore, participants included in the study provided informed consent.

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