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Evaluation of rs2856718 and rs9275572 polymorphisms frequency in the HLA-DQ gene between healthy donors and hepatitis B patients in the Khuzestan province

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Abstract

Introduction: In Asia, chronic hepatitis B is one of the most prevalent infectious diseases affecting public health. Studying the genetic polymorphism of human leukocyte antigen (HLA) is one of the influencing factors in the progression and development of this disease. Most studies have examined the association between HLA-DQ and hepatitis B virus (HBV) infection/clearance, disease progression, and chronic hepatitis B virus infection (CHB) complications.
Objectives: This study investigated the effect of rs2856718 and rs9275572 polymorphisms on HBV patients and healthy individuals.
Materials and Methods: In this study, rs2856718 and rs9275572 were analyzed in 60 patients with chronic hepatitis B and 60 healthy individuals using the tetra-primer amplification refractory mutation system-polymerase chain reaction (TETRA-ARMS-PCR) method.
Results: In this case-control study, 60 patients with CHB, consisting of 43 males and 17 females (71.7% male; 28.3% female; mean: 39.25 ± 9.67 years), and 60 healthy individuals, consisting of 16 males and 44 females (26.7% male; 73.3% female; mean: 32.98 ± 9.58 years), were enrolled. The results indicated that HLA-DQ recessive models, including rs2856718 (OR: 3.281; $P = 0.007$) and rs9275572 (OR: 5.8; $P = 0.015$), significantly increased risk, whereas the rs2856718 co-dominant model (OR: 0.357, $P = 0.006$) correlated with a decreased risk of CHB virus infection.
Conclusion: The results can aid in identifying individuals at risk of HBV infection. The findings may indicate that the HLA-II gene in the host is a determining factor in the outcome of hepatitis B infection. Thus, studying these polymorphisms is recommended, especially in advanced liver disease.

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Introduction

Hepatitis B infection is caused by the hepatitis B virus (HBV), one of the most severe and widespread health issues worldwide. More than a third of the world's population is infected with the virus. Approximately 240 million individuals are at risk for cirrhosis and liver cell carcinoma. Around one million people die annually due to the virus (1). Studies have shown that exposure to the virus does not always result in infection; for instance, in some couples, only one partner has HBV. Currently, the mechanism of stable or cleared hepatitis B is not entirely understood; several factors, including the virus, host genetics, and an individual's level of immunity, may contribute to the variation in response. For example, genetic factors of the host in the HLA system can be cited as a potential cause. Cell-mediated immunity responses are influenced by HLA-I and II polymorphisms that correlate with acute or chronic viral infections (2).

Key point

The rs2856718 and rs9275572 human leukocyte antigen-DQ (HLA-DQ) gene polymorphisms were investigated in this study. Using the TETRA ARMS-PCR method, the frequency of two single nucleotide polymorphisms (SNPs) was determined in chronic hepatitis B patients and healthy individuals. The results revealed that HLA-DQ recessive models, including rs2856718 and rs9275573, increased the risk of HBV infection. Moreover, the rs2856718 co-dominant model was associated with a lower risk of chronic hepatitis B virus infection.

Human leukocyte antigen-DQ (HLA-DQ) is an HLA-II-specific cell surface glycoprotein that transports foreign antigens to T-CD4 cells. This HLA is highly polymorphic, encoding the antigen-binding site in exon 2, where several alleles have been linked to persistent HBV infection (3).

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation in humans and can alter encoded proteins' biological structure and function. Numerous studies have investigated the association between various SNPs and the performance of the HLA system in immune response (1).

In addition, several studies have been conducted on different populations regarding the function of HLA-DQ polymorphisms in complications of HBV infection, which have contradictory and different effects, such as rs2856718 and rs9275319 polymorphisms linked with reduced risk, rs9275572 and rs7453920 polymorphisms associated with increased risk, and rs9272105, which is significantly correlated with the progression of hepatitis B disease in adult liver cancers (1,2,4-9).

Objectives

Since no study examining the frequency of rs2856718 and rs9275572 polymorphisms in the HLA-DQ gene among patients with hepatitis B has been reported in Iran; therefore, the presence of blood recipients such as patients with thalassemia, dialysis patients, and patients related to blood transfusion facilitated our study's objective.

Materials and Methods

Samples

This descriptive epidemiological study included 60 patients with chronic hepatitis B virus infection (CHB) and 60 healthy individuals. Patients were selected for sample collection in 2019 and 2020 via the census. All patients and members of the control group were healthy donors from the Khuzestan province. The subjects were divided into the CHB and healthy control groups. Sixty individuals with CHB were previously diagnosed with chronic active hepatitis using the neutralization method and a Siemens kit (Siemens, Germany).

DNA extraction and purification

Two SNPs (rs2856718 and rs9275572) were selected from the Iranian population. 5 mL of peripheral blood was collected from each patient and stored in Fe (III)-EDTA tubes at -80°C until DNA extraction. Initially, the collected samples' DNA was extracted using desalination. Using a NanoDrop device, the light absorption of each sample was measured to determine the quantity and quality of DNA. All sample concentrations were between 1.8 and 2.0, indicating that the extraction quality was satisfactory. Following sampling and collection of test samples, blood samples were gradually removed from the freezer. Using a Russian amplitude PCR kit, HBV DNA was confirmed, and the link http://primer1.soton.ac was conducted to confirm the required SNPs (Table 1).

TETRA-ARMS-PCR

After designing the primers necessary to determine each SNP, the required materials were gathered and prepared via the following method. The total reaction volume was 25 µL, and the AMPLIQON master mix was employed. The following is the polymerase chain reaction (PCR) temperature protocol for SNPs 9275572 and 2856718: Initial denaturation at 95 °C for 5 minutes, 35 cycles including denaturation at 95 °C for 40 seconds, and annealing at 59 °C and 57.5 °C for 40 seconds for SNP 9275572 and 2856718, respectively. The elongation temperature was 72 °C for 40 seconds; the final elongation temperature was 72 °C after 5 minutes. After removing the samples from the thermocycler, 6 µL of the product was electrophoresed in a 1.7% agarose gel at a voltage of 100 for 45 min, and the bands were analyzed using a QUANTUM gel doc device.

Table 1. Design of primers using the TETRA-ARMS-PCR method

SNP	Primers Name	Sequence
rs2856718(C/T)	Forward inner primer (T allele)	5'CCTCTGGCAGGTTAGGAAGAGCTTTT 3'
	Reverse inner primer (C allele)	5' GAGGACAGGCCATGGGATGAG 3'
	Forward outer primer	5' CCACACCACTGGGGATAAATGAGA 3'
	Reverse outer primer	5' TCTGGAAATTGACCAAAGGATACGAAC 3'
	Product size for T allele	209
	Product size for C allele	313
	Product size of two outer primers	475
rs9275572(G/A)	Forward inner primer (A allele)	5' ATGGTGATTCTGCTCCATAGAAA 3'
	Reverse inner primer (G allele)	5'CTTAGACTAGGTCCTTTAATGACGC 3'
	Forward outer primer	5'GGATAGAAATCCAGGATAAGAAATACA 3'
	Reverse outer primer	5'AAACTTCTTCACAAAGAGTCCCA 3'
	Product size for A allele	151
	Product size for G allele	226
	Product size of two outer primers	329

Statistical analysis

Statistical analysis was conducted using SPSS (version 26) and Haploview software (version 4.2). Statistical significance was determined by a P value <0.05. Subsequently, the Mann-Whitney U test was employed. Furthermore, Hardy-Weinberg equilibrium (HWE) was assessed for each SNP in the non-patient group, and the chi-square test was utilized to determine the absolute magnitude and frequency of genotypes and alleles for each SNP. The relationship between SNPs and susceptibility to HBV infection or disease progression in chronic patients was also evaluated using a two-way cross-sectional table. Afterward, the results were reported regarding the odds ratio (OR) at a 95% confidence interval (CI). The findings were expressed using the following models: the dominant model (AB + BB version AA), the recessive model (BB version AA + AB), and the co-dominant model (AB version AA + BB). A represented the wild-type allele, while B expressed the mutant allele. Using the Haploview software, no correlation was observed between the two polymorphisms.

Results

Subject characteristics

In the present case-control study to evaluate two SNPs (rs2856718, rs9275572), 60 patients with chronic hepatitis B, including 43 males and 17 females (71% male; 28.3% female; mean: 39.25 ± 9.67 years) and 60 healthy individuals, including 16 males and 44 females (26.7% male; 73.3% female; mean: 32.98 ± 9.58 years), were included in the study ($P=0.001$; Table 2). The study of rs2856718 polymorphism with CC, CT, and TT genotypes and rs9275572 polymorphism with GG, GA, and AA genotypes revealed significant differences between patients and healthy individuals ($P=0.011$ and P = 0.022, respectively; Table 3). For the age variable in the patient and non-patient groups, the Mann-Whitney U test indicated a significant ($P=0.001$) difference (Table 2). After statistical adjustment for age and gender, the results indicated that the association between the studied SNPs and the disease was also established (Table 2).

Hardy-Weinberg test results

All samples underwent rs2856718 and rs9275572 genotyping. The genotype frequency of rs2856718 was in HWE in both the patient group and the entire population ($P>0.05$) but not in the control group ($P<0.05$). The frequency of genotypes in rs9275572 was in HWE in the control group and the entire population ($P>0.05$) but not in the patient group ($P<0.05$). Finally, statistical analysis was performed as the whole population of genotypes in rs2856718 and rs9275572 was in HWE ($P>0.05$).

Correlation between rs2856718 polymorphism and HBV infection

Healthy populations and cases of HBV infection were studied based on a 2-in-2 cross-tabulation model. The following describes the relationship between rs2856718 and HBV: Evaluation of genotype frequency in the patient and control group in rs2856718 was significant for the recessive model TT versus CT + CC (OR: 3.281, lower: 1.358, upper: 7.925, $P=0.007$), and the likelihood of developing TT genotype in the patient group was 3.281 times greater than the control group, and TT genotype was effective in disease incidence. Evaluation of genotype frequency in patient and control groups in rs2856718 was significant for CT versus TT + CC co-dominant model (OR: 0.357, lower: 0.170, upper: 0.751, $P=0.006$), and the odds ratio of CT genotype inpatient group was 0.357 times lower than the control group, and CT genotype protected against disease incidence. The study of healthy populations and HBV infection cases revealed the following relationship between rs2856718 and HBV: CT genotype carriers appeared to have a lower risk of hepatitis B infection (OR: 0.357, $P=0.006$), whereas carriers of TT genes demonstrated a strong association (OR: 3.281, $P=0.007$; Table 3).

Correlation between rs9275572 polymorphism with HBV infection

The relationship between rs9275572 and HBV was determined through research on healthy populations and cases of HBV infection using the 2-in-2 cross-tabulation model. Evaluation of genotype frequency in patient and control groups for the rs9275572 gene is significant for the AA Versus AG + GG recessive model (OR: 5.8, lower: 1.213, upper: 27.728, $P=0.015$). The odds ratio for the AA genotype in the patient group is 5.8 times higher than in the control group, and AA genotype carriers increase HBV incidence (Table 3).

Discussion

The pathogenesis of chronic hepatitis, which can result in hepatic cirrhosis and cancer, is one of the world's

Table 2. Demographics of study participants

Variables	Control	Case	*P* value
Age, years, mean± SD	32.98 ± 9.58	39.25 ± 9.67	0.001*
Gender			
Female	44 (73.3%)	17 (28.3%)	0.001**
Male	16 (26.7%)	43 (71.7%)	

P values obtained from Mann–Whitney (*) and 2×2 (**) tests, respectively.

Table 3. Distribution of genotype and allele for HLA gene polymorphisms between patient and control groups

SNPs	Genotype/Allele distribution	Controls	χ2	Patients	OR (95% CI)	*P* value
rs2856718			9.08			**0.011**
	CC	11(18.3%)		13(21.7%)		
	TC	40(66.7%)		25(41.7%)		
	TT	9(15.0%)		22(36.7%)		
	T	62(51.7%)		68(57.5%)		
	C	58(48.3%)		52(42.5%)		
	TT vs CC		1.65		2.068(0.677-6.316)	0.199
	CT vs CC		1.767		0.529(0.205-1.362)	0.184
	C vs T		2.024		1.446(0.869-2.406)	0.155
Recessive	TT vs CT + CC		7.35		**3.281**(1.358-7.925)	**0.007**
Dominant	CT + TT vs CC		0.208		0.812(0.331-1.991)	0.648
CO-Dominant	CT vs CC +TT		7.552		**0.357**(0.170-0.751)	**0.006**
rs9275572			7.669			**0.022**
	GG	31(51.7%)		33(55.0%)		
	GA	27(45.0%)		17(28.3%)		
	AA	2(3.3%)		10(16.7%)		
	G	90(74.2%)		84(69.2%)		
	A	30(25.8%)		36(30.8%)		
	AA vs GG		4.152		4.697(0.953-23.157)	0.042
	GA vs GG		1.752		0.591(0.271-1.290)	0.186
	G vs A		0.739		1.28(0.729-2.248)	0.39
Recessive	AA vs GA + GG		5.926		**5.8**(1.213-27.728)	**0.015**
Dominant	GA + AA vs GG		0.039		0.931(0.457-1.898)	0.844
CO-Dominant	GA vs GG +AA		3.589		0.483(0.227-1.031)	0.058

Risk alleles marked in BOLD letters. OR: odds ratio. The differences in genotype frequencies were analyzed by using a chi-square test. $P \leq 0.05$ was considered to be statistically significant.

most severe health problems. Numerous studies have described the relationship between HLA expression and HBV infection/clearance in various populations and demonstrated that genetic factors of the host play a crucial role in the persistence of this infection. The interaction between gene expression in immune responses and HBV results in subsequent infection-related clinical outcomes (1,10-13).

This case-control study demonstrated for the first time the correlation between rs9275572 and rs2856718 polymorphisms and HBV susceptibility in Khuzestan province (southwestern Iran). The rs2856718-C safe allele (C) was strongly correlated with a reduced risk of chronic HBV infection compared to the BB genotype.

The HLA-DQ recessive models, including rs2856718 (OR: 3.281; $P=0.007$) and rs9275572 (OR: 5.8; $P=0.015$), with an increased risk of HBV infection, and the rs2856718 co-dominant model (OR: 0.357; $P=0.006$), with a decreased risk of HBV infection, were strongly correlated. These findings corroborated with the studies by Tao Xu et al, Xiaowei Ji et al, Lingmin Hu et al, X. Zhang et al, Ahmed A, Al-Qahtani et al, Si-hui Hou et al and Yuka Ochi et al, and also with the study by Tao Xu et al (1, 3, 7, 13-17). However, according to the study by Ahmed A. Al-Qahtani et al, rs9275572-A appears to protect against HBV infection. This study did not support our findings, potentially due to ethnic differences, genetic diversity, and the number of specimens from various groups (15, 18).

Previous studies have shown that epigenetic changes, genetic backgrounds, environmental pressures, geographical locations, and changes in polymorphisms may have different effects on different ethnic groups (8, 19). Several studies in China have demonstrated an association between active immune response variability and HLA polymorphism (20). According to other research, alterations in HLA-DQ molecules may result in viral clearance or the chronic pathogenesis of hepatitis B. Future studies must determine how this diversity affects gene expression and function. Allelic diversity has been reported to be associated with susceptibility to HBV and HCV infections and disease development in different racial populations (8,13). However, the association between HLA, HBV, and HCV infections is quite distinct. SNPs in HBV-related genes have been shown to contribute to an individual's susceptibility to HBV infection by influencing gene expression and function (3,21,22).

Our findings revealed a significant correlation between male and female gender variables. Nonetheless, this gender disparity is well established in HCC patients with chronic hepatitis for example in the study by Bush et al (23). As a result, in the future, more emphasis should be conducted on gender composition and genetic differences in CHB to understand the mechanism of host HBV infection better.

Conclusion

This study demonstrated that genetic variations in HLA-

DQ genes are associated with chronic hepatitis B in the Khuzestan province population (southwestern Iran). Our findings may contribute to a better understanding of the pathogenicity of hepatitis B polymorphisms rs2856718 and rs9275572 and better clinical outcomes of the disease. Future research could investigate the relationship between other polymorphisms and HBV in other geographical regions of Iran. By studying the connection between the HLA system and HBV infection, strategies can be developed for identifying populations at risk for HBV infection. However, additional testing is necessary to confirm the impact of genetic factors. Moreover, these findings hold promise for the development of patient-specific therapeutic interventions.

Limitations of the study

This study conducted in a limited area (the Khuzestan province). We suggest further investigations on large populations of different ethnicities.

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Authors' contribution

Conceptualization: Gholam Abbas Kaydani.
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Visualization: Fereshteh Moeinyzadeh.
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Writing–review & editing: Fereshteh Moeinyzadeh.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved this research (Ethical code#IR.AJUMS.REC.1397.912). This study was conducted on blood transfusion samples from Khuzestan, on which routine tests were completed. Patients were provided written consents during their hospital admission. This study was extracted from Fereshteh Moeinyzadeh's MSc thesis at Ahvaz Jundishapur University of Medical Sciences (Thesis# Alef K/205). The authors thoroughly considered ethical considerations (including plagiarism, data forgery, and duplication).

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The data supporting this study's findings are included in the manuscript and will be available after publication.

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