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Association of IL-28B (rs12979860) Gene Polymorphism and Serum IL-28B Levels with Chronic Hepatitis B Infection

Hussain Naeim Mohammed[1], **Alaa Ali Matrood**[1*]

[1]Department of Biology, College of Science, Wasit University, Wasit, Iraq

Abstract

Introduction: Hepatitis B virus (HBV) infection remains a major public health issue. The progression is contingent on various factors, including immunogenetic elements. This study aimed to examine the association between interleukin 28B gene (IL28B) diversity and the advancement of this infection.

Methods: This retrospective case-control study included 64 individuals with chronic hepatitis B virus infection. Infection, 39 in the HBV group and 31controls. The analysis of IL28B the Tetra-primer ARMS-PCR was used to test for promoter polymorphisms. SNPs (rs12979860) of IL28B. IL28B for every patient with a persistent HBV infection, levels were determined using an internal ELISA, or Enzyme-Linked Immunosorbent Assay HBV clearance and control groups.

Results: Three genotypes were found using allele polymorphism analysis: CC (48.5%), CT (35.9%), and TT (15.6%) in HBV patients. The The only genotype that was significantly more prevalent in control group was CC (OR=0.38; CI95% [0.16-0.95]; $P=0.04$). In contrast with patients with HBV, the IL28B level was significantly higher in the control group (14.5±4.6 vs. 12.6±9.2, 7.5±2.2 ng/L: $P=0.001$). Significantly elevated IL28B levels were also associated with a lower HBV viral load ($P=0.001$).

Conclusion: These results suggest that the CC genotype has a potential protective role against HBV infection, while the TT genotype may be associated with higher vulnerability.

Keywords: Chronic Hepatitis B virus, Serum IL-28B, Interleukin 28B

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Introduction

Worldwide, Infection with the hepatitis B virus (HBV) is a major public health risk. There are about 1.23 million new instances of infection. recorded The yearly, with 63% of those cases occurring (1). HBsAg is the surface antigen of hepatitis B.was projected to be present in 291 million people worldwide in 2016; approximately 5% of adult-aged HBV infections develop into chronicity and endure (2). Persistent HBV infection is a serious issue that leads to significant morbidity and mortality, together with serious consequences such cirrhosis and hepatocellular carcinoma (HCC). Indeed, the World Health Organisation (WHO) anticipates that 1.1 million deaths occurred worldwide in 2022 (1). Infection with the hepatitis B virus (HBV) outcomes are influenced by cytokines, which are essential in mediating effective innate and adaptive immune responses(3,4). Particularly important for defence against a variety of infections is the interferon (IFN) cytokine family (5). Hepatitis C infection spontaneous clearance and viral load are closely associated with IL28B gene polymorphisms, according to numerous investigations. The cytokine IFN-lambda3 (INF-λ3), a member of the type III interferon family (INF-λ), is encoded by the IL28B gene (6). Through a network of genes triggered by infections and autoimmune illnesses, interferon-lambdas (IFN-λs) regulate immunity. When IFN-λs interact with the heterodimeric IFN-λ receptor. (IFN-λR), a signal cascade dependent on STAT phosphorylation is triggered. As a result, IFN-stimulated genes in the hundreds are produced, and through feed-forward and feedback loops, this complex modifies different immunological activities. The clinical progression and therapeutic results of hepatitis B and C viral infections have been linked to the genetic variations as a series of single-nucleotide polymorphisms (SNPs) associated with genes participating in the IFN-λ signalling pathway.(7). The IL-28B gene has single nucleotide polymorphisms (SNPs) at loci rs12979860, that are 3 kilobases upstream of the gene and have recently been linked to how certain people react to viral infections (8;9). Both of the responsiveness to antiviral therapy and the spontaneous removal of HCV have been linked to the IL-28B polymorphisms, which are crucial for the infection's resolution. Genetic variations of IL-28B may potentially possess a functional role during chronic HBV infection because HBV and HCV share comparable natural histories, levels of pathogenicity, and routes of transmission (10). The dearth of knowledge on the connection between HBV infections and the genetic profile of IL-28B led to this investigation. Thus, this study's main goal was to investigate any potential

*Corresponding Author: Alaa Ali Matrood, Emails: amatrood@uwasit.edu.iq

correlation between the HBV polymorphism rs12979860 and the infection's clinical symptoms.

Materials and methods

Study population

This study included 134 human samples, including 64 samples from patients with HBV infection (33 males and 31 females) who were diagnosed by a specialist physician based on clinical symptoms, physical signs, and confirmed Positive Hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) infection test results, with an age range of 13 to 75 years. Additionally, 39 samples from Hepatitis B surface antibody (HBsAb) and patients who tested positive for hepatitis B core antibody recovered from HBV infection (HBcore Ab) an additional 31 health samples were collected as the control group. The samples were gathered from Al-Karama Teaching Hospitals, the Viral Hepatitis Testing Center at Al-Zahraa Teaching Hospital, and the General Public Health Central Lab in Kut City in Wasit Province.

plasma preparation

Venous blood samples were collected from 134 individuals, including 64 patients diagnosed with HBV infection, 39 with HBV clearance, and 31 healthy subjects serving as the control group. Each participant had approximately 5 mL of blood drawn into EDTA tubes containing an anticoagulant. The samples were centrifuged for ten minutes at 3000 rpm, and the clear plasma was carefully separated to avoid cellular contamination and transferred into sterile, labeled Eppendorf tubes. Until analysis, serum samples were stored at -20 °C..The concentration of IL-28B was determined according to the manufacturer's recommendations using commercially available ELISA kits.

laboratory diagnosis

After blood collection and centrifugation, the laboratory diagnosis of enzyme-linked immunosorbent tests were used to measure Hepatitis B core antibody (HBcAb), hepatitis B surface antigen (HBsAg), and hepatitis B surface antibody (HBsAb) levels. (ELISA) for patients who recovered from HBV. The Hepatitis B virus (HBV) viral load was calculated using positive cases (HBsAg) identified by ELISA. An automated extraction device was used to obtain DNA for the HBV viral load testing. (Viral nucleic acid extraction kit, Zybio, China). Subsequently, HBV DNA viral load quantification was performed using the Viral Load HBV Quantification Kit (Sacace, Italy) on the qRT-PCR BIORAD (BIO-RAD Laboratories, Hercules, CA, USA) CFX-96 system.

Detection of IL -28B levels

Serum levels of interleukin-28B (IL-28B) was quantitatively determined using the enzyme- assay using linked immunosorbent (ELISA). Sandwich ELISA kits that are sold commercially were used in accordance with the manufacturer's recommendations. In summary, the Microelisa stripplate included this kit has been pre-coated with an IL28B-specific antibody. Samples or standards are mixed with the particular antibody after being added to the proper Microelisa stripplate well Each Microelisa stripplate the well is then filled with an IL28B-particular Horseradish Peroxidase (HRP)-conjugated antibody, which is then incubated. Free elements are removed by washing. The TMB substrate solution is added to each well. After adding the stop solution, only the wells with IL28B and HRP conjugated IL28B antibody will turn blue prior to becoming yellow. The optical density (OD) is measured at 450 nm using spectrophotometry.The OD value is directly correlated with the IL28B concentration. By comparing the samples' OD to the standard curve, you may determine the IL28B concentration in the samples.

Genomic DNA analysis

Geneaid genomic DNA was used to extract genomic DNA from peripheral blood leukocytes. Purification (Taiwan) kit and stored at −20 °C. For stored of DNATwo microliters of extracted DNA samples were placed into a spectrophotometer with a micro-volume. (Bio photometer plus) with the absorption ratio calibrated at 260 and 280 nm to ascertain the concentration and DNA purity. The mean concentration ranged from 50 to 70 µg/ml, and the purity (OD 260/OD 280) of all genomic DNA samples was determined to be between 1.7 and 1.9IL-28B (rs12979860) was genotyped via the tetra-primer ARMS PCR assay. One well-known procedure for SNP genotyping is the tetra-primer amplification refractory mutation system (ARMS) polymerase chain reaction (PCR) Regardless of the target gene's genotype, the outer primers amplify a sizable portion of it in a one-step reaction.However, Each inner primer pairs with a corresponding outer primer to generate smaller, allele-specific amplicons of differing sizes, which may be easily identified as homozygous or heterozygous using gel electrophoresis.(11).

Primer design, method validation, and genotyping

(rs12979860) SNP genotyping was completed using the tetra-primer ARMS-PCR technique. This straightforward, rapid, and sensitive technique can be used to detect single nucleotide polymorphisms. The four primers used for forward outer, reverse outer, forward inner, and reverse inner. For T-ARMS-PCR are the four primers utilised inside this process.For the IL28B rs12979860 polymorphism, we employed two external primers: front outer "5-GTCACTCACGCAGGCCGCCACATC-3" and reverse outer "5- ACCGCTACGTAAGTCACCGCCCAGCC-3". Additionally, we utilized two allele-specific internal primers: forward inner for the C allele "5- CGGAGTGCAATTCAACCCTGGTGCG-3" and reverse inner for the T allele "5-CTGAACCAGGGAGCTCCCCGAAGGAGT-3"(12).

Polymerase chain reaction (PCR) was performed. Employing a commercially accessible PCR master mix (Go Taq Green Master Mix; Promega, Daejeon, USA) in compliance with the manufacturer's recommended methodology. In a 0.2-mL PCR tube, 12.5 µL of Go Taq

Green Master Mix (2X), 5 µL of template DNA, 0.5 µL of each primer (10 µM), and 5.5 µL of DNase-free water were added. The PCR cycling parameters were an initial 5 minutes at 95°C, followed by 35 cycles of 30 s at 95°C. 40 s at the 62°C and 60 s at 72°C, culminating in a final extension at 72°C for 8 min. Each reaction was confirmed on a 2% agarose gel containing ethidium bromide.Various sizes of amplification bands were observed following the completion of tetra-primer ARMS-PCR. For the rs12979860 SNP, we discovered fragments of 317, 473, and 738 bp. (Figure 1).

Statistical methods

The statistical difference between patients with HBV, HBV clearance, and controls was assessed using a chi-squared test. The Hardy-Weinberg equilibrium (HWE) was assessed using Fisher's exact test for each SNP in the control group. The 95% confidence intervals (CIs) and odds ratios (ORs) were computed using regression logistic models adjusted for confounding factors for genotype analysis. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SPSS statistical software suite.

Results

The distribution of age and sex among patients with hepatitis B infection, HBV clearance, and healthy controls is presented in Table 1. The greatest proportion of (51.7%) was age ≥ 50-years old, followed by (21.8%) at age < 30-years old, (18.7%) at age 40–49-years old, and (7.8%) 30–39-years old in patients with HBV Likewise, the sex distribution showed significant difference ($P = 0.002$) , as males constituted 51.6% of the patient group, 64.2% of HBV clearance group, and 51.7% of the controls, whereas females represented 48.4%, 35.8%, and 48.3%, respectively. Overall, no notable variations were observed among the three groups with respect to age.($P > 0.05$ for all). However, regarding sex, the results showed significant differences ($P = 0.002$), indicating that cases, clearance, and controls were generally well-matched for these demographic variables.

Statistical analysis revealed a considerable increase ($P < 0.001$) in the serum level of IL-28B in the control in compared to the HBV patients and clearance illustrated in Table 2. The mean IL-28B levels were 14.5 ± 4.6 for controls, 12.6 ± 9.2 for HBV clearance, and 7.5 ± 2.2 for HBV patients.

Significant differences between the serum concentration of IL-28B and HBV viral load ($P = 0.004$) are shown in Table 3. Statistical analysis indicated substantial differences in the serum IL-28B level and HBV viral load. The mean IL-28B levels were 9.03 ± 1.7 for low viremia, 7.31 ± 2.1 for moderate viremia, and 6.59 ± 2.3 for high viremia.

Among HBV patients the genotype frequencies were CC (48.5%), CT (35.9%), and TT (15.6%). In the control group the CC genotype was predominant (70.9%), followed by CT (22.6%) and TT (6.5%), Table 4 The increased CC genotype prevalence in the control group contrasted with HBV patients suggests a potential protective role of this genotype against HBV infection. Conversely, the CT and TT genotypes appeared more frequent among HBV patients, indicating a possible association with increased susceptibility. The genotype distributions The data for both HBV patients and controls adhered to Hardy-Weinberg equilibrium ($P > 0.05$). This indicates genetic stability within the studied population and confirms the absence of significant genotyping errors, selection bias, or population stratification. Compliance with Hardy–Weinberg equilibrium supports the reliability from the genotyping data and validates its suitability for association analysis. The prevalence of the C allele was greater in the control group. (82.2%) compared with HBV patients (66.4%), whereas the T allele was more prevalent in patients with HBV (33.5%). more than in controls (18%). This difference implies that the C allele might be connected

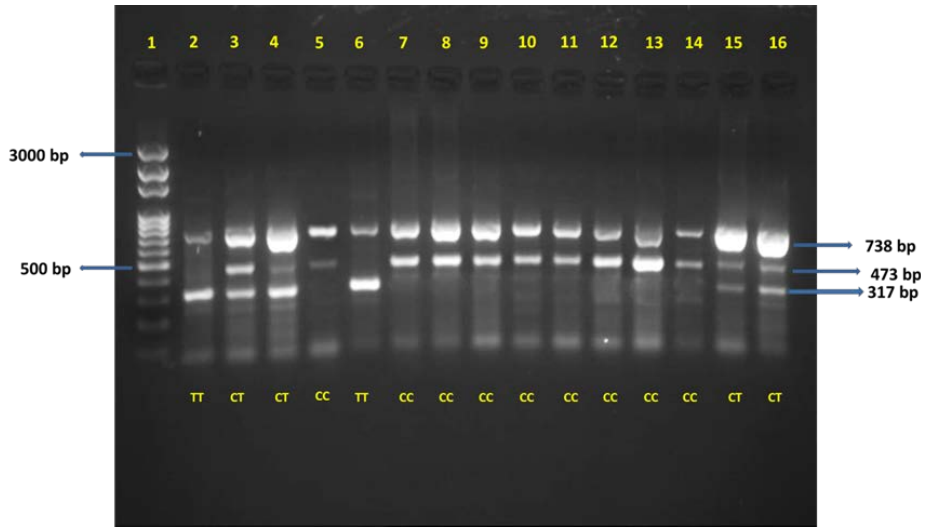

Figure 1. An image of agarose gel electrophoresis displaying the examination of PCR products. IL28B (rs12979860) gene polymorphism from plasma samples in HBV patients. Lane 1 (Marker ladder 100-3000bp). Lane (3,4,15,16) carrying heterozygote genotype (CT) ≈ 473 bp , Lane (5,7,8,9,10,11,12,13,14) carrying wild type homozygote genotype (CC) ≈ 738 bp and Lane (2,6) carrying homozygous mutant genotype (TT) ≈ 317 bp ; separated on Agarose (2 %)

Table 1. Age and sex distribution of investigated subjects with Hepatitis B infection

Indicators		Patients (No. = 64)		Control (No. = 31)		Clearance (No. = 39)		*P* value (Sig.)
		Freq.	%	Freq.	%	Freq.	%	
Age/Years	<30-year, n (%)	14	21.8	10	32.2	8	20.5	0.28 (N.S)
	30–39-year, n (%)	5	7.8	5	16.1	7	17.9	
	40–49-year, n (%)	12	18.7	9	29	3	7.6	
	≥50-year, n (%)	33	51.7	7	22	21	53.8	
Sex	Male, n (%)	33	51.6	16	51.7	25	64.2	0.002** S
	Female, n (%)	31	48.4	15	48.3	14	35.8	

n: number of instances; NS: not significant at $P > 0.05$; S: significant at $P \leq 0.05$; ** Significant differences

Table 2. Evaluation of Human IL-28B concentration in patients, HBV clearance and controls

	IL-28B (ng/L)			
Groups	**Patients with HBV n = 64**	**control n = 31**	**Clearance HBV n = 39**	***P* value**
Mean ± SD	7.5 ± 2.2	14.5 ± 4.6	12.6 ± 9.2	<0.001**

Table 3. The relationship between HBV viral load and IL-28B blood concentrations

	HBV patients n = 64			
HBV DNA Viral load (IU/ml)	**Low viremia n = 27**	**Moderate viremia n = 20**	**High viremia n = 17**	***P* value**
IL-28B (ng/L)	9.03 ± 1.7	7.31 ± 2.1	6.59 ± 2.3	0.004

Table 4. Observed and expected genotype with HBV patient and control group allele frequencies

IL28B (rs12979860)										
T Allele	C Allele	(chi2)	Alleles		HWE *P* < 0.05	Genotypes			Groups	
			T	C		TT	CT	CC		
			43	85	N.S.	10	23	31	NO. Observed	HBV (n: = 64)
			33.5	66.4		15.6	35.9	48.5	%	
0.33	0.66	2.42	Not estimated			7.22	28.55	28.22	NO. Expected	
						11.2	44.6	44	%	
			11	51	N.S.	2	7	22	NO. Observed	control (n: = 31)
			18	82.2		6.5	22.6	70.9	%	
0.17	0.82	1.588	Not estimated			0.98	9.05	20.98	NO. Expected	
						3.1	29.1	67.6	%	
			2.35	0.043		2.69	1.92	0.38	Odds Ratio (OR)	
			0.02	0.02		0.3	0.2	0.04	Fishers Exact Probability	
			1.12-4.93	0.2-0.9		0.56-12.78	0.73-5.08	0.16-0.95	95% Confidence interval (C.I.)	

to with resistance to HBV infection, while the T allele may contribute to increased susceptibility. Statistical analysis revealed a substantial correlation between a reduced risk of HBV infection and the CC genotype (OR = 0.38, $P = 0.04$, 95% CI = 0.16–0.95), demonstrating a protective impact. In contrastthe genotype of CT (OR = 1.92, $P = 0.2$) and TT genotype (OR = 2.69, $P = 0.3$) revealed no meaningful correlation with HBV susceptibility. At the allelic level, the C allele demonstrated a protective association (OR = 0.43, $P = 0.02$), In contrast, the T allele was linked to a higher risk. of HBV infection (OR = 2.35, $P = 0.02$). These findings propose that the presence of the T allele may predispose individuals to HBV infection, while the C allele may confer partial protection.

Discussion

IL28A, IL28B, and IL29 are three cytokine genes that are members of the IFN-λ (also known as type III IFN) family and are encoded by the chromosomal region 19q13. When IFN-λs engage with transmembrane receptors, they activate the JAK-STAT and MAPK pathways, resulting in strong antiviral responses.(13;14). The importance of IFN-λs in the immune response and the upregulation of transcription of IFN-stimulated genes necessary to suppress viral infections, including herpes simplex, HIV, and B and C viruses, have been shown in both in vivo and in vitro models (15,16), HIV (17), as well as the B and C viruses (18,19). The outcome of HCV infection is significantly influenced by IL28B-associated polymorphisms, according to earlier research. (20). In particular, the rs12979860 polymorphism, also referred to as the IL28B variant, is linked to both spontaneous and IFN-α treatment-induced HCV eradication, and was found to be the most reliable indicator of peginterferon

treatment results. (21,22). In fact, this variation has been linked to resolution of HCV infections and elevated serum levels of IL29 and IL28A/B.(23). Our study's findings demonstrated that patients with HBV had lower serum levels of IL-28B than those without. Clearance and control group, results of the present the study aligns with prior findings. studies conducted in Iraq, including (24). A 2015 study (25) found that the Levels of IL28B protein and IL28A/B mRNA expression in the blood were lower in patients with CHB, fibrosis, and HCC than in inactive and healthy carriers. Similar findings were reported by (9) who demonstrated reduced expression of IL-28B in both healthy people and individuals with chronic hepatitis B virus infection. The current investigation revealed a statistically significant adverse relationship. Between serum interleukin-28B (IL-28B) levels and HBV viral load ($P = 0.004$). Patients with low viremia exhibited the highest IL-28B concentrations, whereas progressively Reductions were noted. In moderate and high viremia groups. This arrangement suggests that increased viral replication is associated with impaired IL-28B–mediated immune responses. Our study's findings are consistent with this study(25) that reported significantly reduced IL-28B expression and protein levels in individuals with either active or progressed HBV illness compared with inactive carriers and healthy controls, suggesting that decreased IL-28B is associated with enhanced viral activity and disease progression. According to these studies (9;24) that finding Serum IL-28B levels generally show an inverse correlation with Hepatitis B Virus (HBV) viral load, indicating that higher IL-28B levels are associated with lower HBV DNA, aiding viral control, whereas lower levels are found in chronic infection. An extended arm of chromosomal number 19 (q13) contained three cytokines (IL28A, IL28B, and IL29), according to a genome-wide association study. Among these cytokines, IL28B is a part of the IFN-λ family that stimulates interferon-stimulating genes (ISGs) to trigger viral responses. This cytokine was found to be the primary component of the immune response in earlier research, and it has a strong correlation with treating CHC infection. (13,15,26). Only a few research have shown that IL28B genetic variations are positively correlated with HBV infection. (27) Discovered that among Chinese HBeAg positive CHB patients, The IL28B haplotype block AC (rs12980275/rs12979860) was associated with an elevated response rate to PEG-IFN therapy. Furthermore, a greater rate of seroconversion to an HBsAg (-) status was linked to IL28B haplotype block CG (rs12979860/rs8099917). (28). The results of current study showed the CC genotype higher in control group compared than patients. The increased CC frequency genotype in the control group comparing with HBV patients suggests a potential protective role of this genotype against HBV infection. In the control group, the C allele was more common. (82.2%) compared with HBV patients (66.4%), whereas the T allele was more common in individuals with HBV (33.5%) more than in controls (18%). This variation implies that the C allele might be connected to resistance to HBV infection, while the T allele may contribute to increased susceptibility. The results of the present investigation are supported by several previous investigations that reported a beneficial role of the CC genotype of rs12979860.(29) Demonstrated that individuals with HBV or HCV infection are protected from developing hepatocellular carcinoma (HCC) by the IL28B rs12979860 CC genotype. Similarly, (30) shown that individuals with the CC genotype exhibited greater ability to clear HBV compared with the genotypes TT and CT in a Pakistani population. Furthermore (31-35) revealed that the CC IL28B rs12979860 genotype Considerably improved persistent virological interferon-treated HBeAg-negative chronic hepatitis B patients' response and HBsAg clearance.

Conclusion

The current study demonstrates an elevated rate of infection with viral hepatitis B among patients. Interleukin 28B was much higher. In the control group than in the HBV patients. The current study demonstrated an inverse correlation between interleukin-28B levels and viral load. They had no significant differences among IL-28B (rs12979860) polymorphism also HBV susceptibility. IL-28B (rs12979860) genotype CC was the most frequent in the control group. The polymorphism of (rs12979860) in the IL-28B promoter regions was determined and reported a relation of this polymorphism with the HBV patient group.

Authors' Contribution

Conceptualization: Hussain Naeim Mohammed, Alaa Ali Matrood
Data curation: Hussain Naeim Mohammed
Formal analysis: Hussain Naeim Mohammed
Funding acquisition: Hussain Naeim Mohammed
Investigation: Hussain Naeim Mohammed
Methodology: Hussain Naeim Mohammed
Project administration: Hussain Naeim Mohammed, Alaa Ali Matrood
Resources: Hussain Naeim Mohammed, Alaa Ali Matrood
Software: Hussain Naeim Mohammed
Supervision: Hussain Naeim Mohammed
Validation: Hussain Naeim Mohammed
Visualization: Hussain Naeim Mohammed
Writing – original draft: Hussain Naeim Mohammed, Alaa Ali Matrood
Writing – review & editing: Hussain Naeim Mohammed, Alaa Ali Matrood

Competing Interests

The writers affirm No conflicting interests, either monetary or not.

Data Availability of Statement

The datasets produced and examined throughout the current study is not accessible to the general audience because respect privacy of participants as well as privacy issues however, with reasonable request, can be obtained from the relevant author.

Ethical Approval

Ethical clearance for the research was provided by the relevant institutional ethics committee prior to the commencement of sample collection.

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