ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20230355

# Relationship between IL-17, TNF-α, IL-10, IFN-γ, and IL-18 polymorphisms with the outcome of hepatitis B virus infection in the Turkish population

Esra Nurlu Temel[1*], Fusun Zeynep Akcam[1], Vildan Caner[2], Gülseren Bagcı[2], Muhammet Yusuf Tepebası[3]

## SUMMARY

**OBJECTIVE:** Hepatitis B virus is a global threat that can lead to liver cirrhosis and hepatocellular carcinoma. For the treatment of chronic hepatitis B virus, polymorphisms might be an option for gene treatments. This study aimed to investigate the effects of IL-17, TNF-α, IL-10, IFN-γ, and IL-18 gene polymorphisms on hepatitis B virus infection in the Turkish population.

**METHODS:** The genotypes and allele distribution of 75 patients exposed to hepatitis B virus and 50 healthy control individuals were analyzed. The real-time polymerase chain reaction method was used for identification.

**RESULTS:** A correlation was observed between susceptibility to hepatitis B virus infection and IL-17 Exon 3/3'UTR (rs1974226) C, IL-17 Exon 3 (rs763780) A, IL-18 (-607) (rs1946518) A alleles, and IL-17 Exon 3 (rs763780) AA genotype (p=0.006, p=0.009, p=0.025, and p=0.008, respectively). Furthermore, IL-18 (-137) (rs187238) TT genotype and TNF-α-308 (rs1800629) G and A alleles, were associated with protection against hepatitis B virus infection (p=0.0351 and p=0.032, respectively).

**CONCLUSION:** This study demonstrated that TNF-α (-308), IL-17 (Exon 3/3' UTR), IL-17 (Exon 3), and IL-18 (-607) polymorphisms are associated with hepatitis B virus infection. Therefore, these may serve as potential therapeutic targets for chronic viral hepatitis in the Turkish population.

**KEYWORDS:** IL-17. TNF-alpha. IL-10. IFN-gamma. IL-18. Hepatitis B.

## INTRODUCTION

Hepatitis B virus (HBV) continues to be a global health burden despite the availability of highly protective vaccines and effective antiviral drugs. The World Health Organization reported that, in 2019, 820,000 people died of cirrhosis and liver cancer, and 296 million were chronic hepatitis B patients[1].

The dynamics between virological, environmental, and host genetic factors determine the outcomes of HBV infection[2]. In some individuals, the host response is viral clearance against HBV infection, whereas the reason for developing chronic HBV infection in other individuals is unknown. This difference has been associated with single-nucleotide polymorphisms (SNPs) in the regulatory region of cytokine genes. Genetic variations such as SNPs, which cause cytokine structure and expression changes, can increase the risk of infection and affect disease outcomes and treatment responses[3].

Among cytokines, IL-17 synthesized by the next-generation T helper 17 (Th17) cells plays a critical role in the pathogenesis of chronic HBV[4]. In cases of chronic HBV, a significant increase in the blood levels of Th17 cells and a rise in the number of Th17 cells in liver tissue in proportion to the hepatitis activity index have been observed[5]. However, few studies have investigated the relationship between HBV and IL-17 SNPs. Unlike IL-17, polymorphisms in the TNF-α are the best-characterized genetic variations associated with HBV[6]. Park et al. found that the antiviral effect of TNF-α was associated with the activity of p22-FLIP (cellular FLICE inhibitory protein), which restricts the HBV life cycle by inhibiting HBV DNA replication[7]. Furthermore, TNF-α SNPs could be important genetic biomarkers for liver pathogenesis[8].

In chronic HBV, a new subset of regulatory B (Breg) cells that can regulate CD8+T cell immunity and produce IL-10

[1]Suleyman Demirel University, School of Medicine, Department of Infectious Diseases – Isparta, Turkey.
[2]Pamukkale University, School of Medicine, Department of Medical Genetics – Denizli, Turkey.
[3]Suleyman Demirel University, School of Medicine, Department of Medical Genetics – Isparta, Turkey.
*Correspondence author: dresratemel@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 25, 2023. Accepted on May 07, 2023.

was identified. Increased IL-10 levels with Breg cell number in chronic HBV were associated with viral load and liver inflammation dynamics[9]. In support of this information, IL10 SNPs have been reported to be associated with the chronicity of hepatitis B and liver damage caused by HBV[10]. Like TNF-α, IFN-γ suppresses HBV replication in infected cells and reduces viral load by activating the antiviral effect of CD8+T lymphocytes[11]. The IFN-γ +874T/A polymorphism has been associated with HBV risk, particularly in the East Asian population[12]. IL-18, known as a potent inducer of IFN-γ, was found to be associated with the Th1 polarization of HBV-specific T cells and promote viral clearance[13]. In many studies, IL-18 polymorphisms have also been associated with susceptibility to HBV and reported to have a therapeutic value[13].

Viral hepatitis clinical outcomes vary in different populations, and genetic background is likely one of the reasons behind the differences. Genetic variability could be utilized to predict disease outcomes and treatment responses. Turkey is in the middle endemic region of the world in terms of HBV infection[14]. However, just several studies on this subject have been conducted in the region. Therefore, this study aimed to evaluate the effect of SNPs in IL-17, TNF-α, IL-10, IFN-γ, and IL-18 gene regions on the clinical course of HBV infection in the Turkish population.

## METHODS

The study group included patients who were followed up for HBV infection for at least 18 months or longer in Suleyman Demirel University Faculty of Medicine, Infectious Diseases polyclinic. According to the criteria, 75 patients exposed to HBV and 50 healthy individuals were included in the study[15]. Patients group were classified into subgroups as "naturally immune," "inactive carriers," and "chronic active hepatitis." Individuals co-infected with hepatitis C and D and human immune deficiency virus and patients with different chronic liver diseases were not included in the study. The study was carried out with the approval of the Suleyman Demirel University Faculty of Medicine Ethics Committee (2/14). Informed consent was obtained from all participants, and the research protocol was performed in accordance with the ethical rules of the Declaration of Helsinki.

### DNA Isolation

Peripheral venous blood samples taken from the individuals in the study group were transferred to tubes containing ethylene diamine tetra acetic acid (EDTA). Genomic DNA was extracted from a 200 μL peripheral venous blood sample according to the manufacturer's recommendations (High Pure PCR Template Preparation Kit, Roche). Isolated DNA samples were stored at -20°C for use in real-time polymerase chain reaction (RT-PCR) analysis.

### Identifying polymorphisms

RT-PCR was used to identify SNPs in the IL-17, TNF-α, IL-10, IFN-γ, and IL-18 gene regions. The Light Cycler 2.0 RT-PCR system (Roche, Germany) was used for SNP analysis in accordance with protocols specified by the manufacturer. For DNA amplification, target site-specific primers and hybridization probe sequences (TIB Molbiol, Berlin, Germany) were designed.

## RESULTS

Allelic and genotypic distributions of SNPs in the HBV-infected case group and the healthy control group included in the study were analyzed. Allelic distributions of the patient and control groups were determined by RT-PCR melting curve data according to polymorphisms (Figure 1).

The frequency of the TNF-α (-308) G and A alleles was higher in the control group than in other groups, especially significantly considerably higher when compared with the group that was naturally immune to HBV (p=0.032) (Table 1).

When the control group and all patients group were compared, we found that IL-17 (Exon 3/3' UTR) C allele was more common in the all-patients group infected with HBV and the A allele in the control group, and the difference was statistically significant (p=0.006) (Table 1). Also, in subgroup analysis (according to their clinical status), a comparison of the patient groups with control group showed that the C allele was more common in natural immune and asymptomatic carriers, while the A allele in control group had a statistically significant difference (p=0.033 and p=0.018, respectively) (Table 1).

The IL-17 (Exon 3) A allele was found to be expressed at higher levels in all patients infected with HBV group compared to the control, and the G allele was found to be expressed at a higher level in control group (p=0.0099) (Table 1). In genotype association analysis between control and all-patient groups infected with HBV, IL-17 (Exon 3) AA (homozygous wild type) genotype was observed at a higher frequency and statistically significant in the all-patient group (p=0.008). In subgroup analysis, IL-17 (Exon 3) AA genotype was more common in the naturally immune to HBV and asymptomatic carriers' groups compared to the control group (p=0.045 and p=0.045, respectively). Conversely, IL-17 (Exon 3) AG (heterozygous) genotype was observed at a lower frequency in the groups, naturally immune to HBV, asymptomatic carriers, and

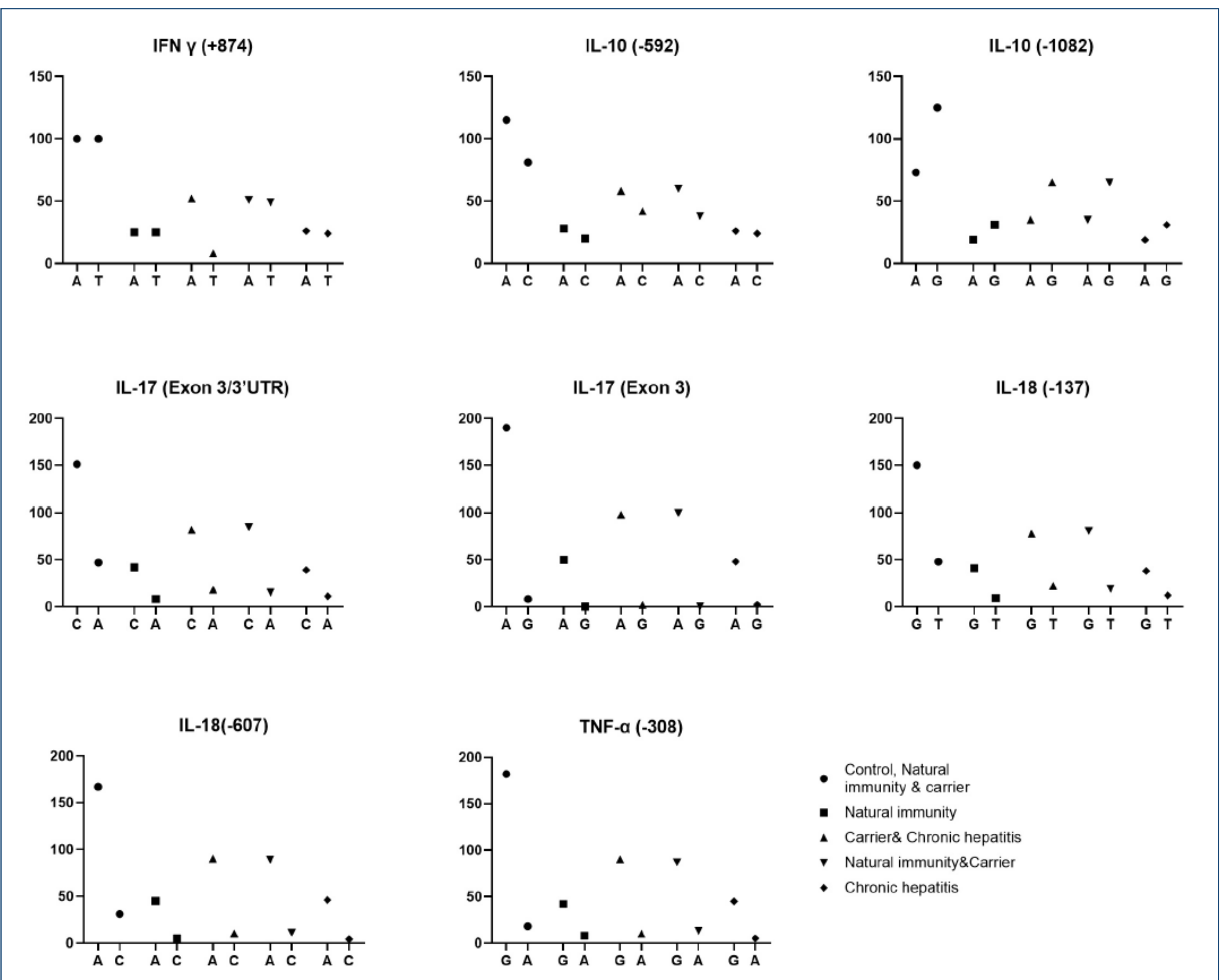


**Figure 1.** Allele distribution graph in the created groups.

all patients infected with HBV groups than the healthy control group (p=0.045, p=0.045, and p=0.008, respectively) (Table 2).

We determined that IL-18 (-607) C allele significantly increased in the group of patients infected with HBV, while the A allele increased in the control group (p=0.025) (Table 2). Moreover, there was no noticeable difference in allele level for IL-18 (-137), whereas, in the genotype association analysis, the CC genotype was significantly higher in the control group compared to the group with all HBV-infected patients (Table 2).

## DISCUSSION

The development of molecular genetics has stimulated studies evaluating the impact of human genome variability on immune response and disease mechanisms. Numerous studies have shown that cytokine gene polymorphisms have an impact on the prognosis of HBV infection in the general population[3,16]. Our study revealed that TNF-α (-308) G and A alleles, which were found to be higher in the healthy control group than in subjects exposed to HBV, were associated with protection against HBV. However, no significant relationship was found between the genotypic level of TNF-α (-308) G/A polymorphism and HBV infection. Unlike our results, the TNF-α (-308) G allele was found to be higher in the chronic hepatitis group in two studies conducted in Turkey[17,18]. In a meta-analysis by Zhang et al. in which studies conducted on the Chinese population were compiled, the TNF-α (-308) A allele was associated with a decrease in the chronicity of HBV, similar to our study[19]. In addition to these results, in a Brazilian study, the TNF-α (-308) A allele and AA genotype were associated with

**Table 1.** Allele distribution, frequencies, and statistical analysis between the control and patient groups.

| Gene | Allele | Control (2n=100) (F) OR (95%CI) | Natural immunity (2n=50) (F) p-value OR (95%CI)[a] | Carrier (2n=50) (F) p-value OR (95%CI)[b] | Chronic hepatitis (2n=50) (F) p-value OR (95%CI)[c] | All patients (2n=150) (F) p-value OR (95%CI)[d] |
|---|---|---|---|---|---|---|
| TNF-α (-308) rs1800629 | G | 95 (0.95) | 42 (0.84) | 45 (0.9) | 45 (0.9) | 132 (0.88) |
| | A | 5 (0.5) | 8 (0.16) | 5 (0.1) | 5 (0.1) | 18 (0.12) |
| | NA | 0 | 0 | 0 | 0 | 0 |
| | | | p=0.032 3.61 (1.11–11.71) | p=0.302 2.11 (0.58–7.66) | p=0.302 2.11 (0.58–7.66) | p=0.074 2.59 (0.92–7.22) |
| IFN-γ (+874) rs2430561 | A | 49 (0.49) | 25 (0.5) | 26 (0.52) | 26 (0.52) | 77 (0.51) |
| | T | 51 (0.51) | 25 (0.5) | 24 (0.48) | 24 (0.48) | 73 (0.49) |
| | NA | 0 | 0 | 0 | 0 | 0 |
| | | | p=10.96 (0.49–1.89) | p=0.862 0.88 (0.45–1.75) | p=0.862 0.88 (0.45–1.75) | p=0.796 0.91 (0.55–1.51) |
| IL-10 (-592) rs1800872 | A | 55 (0.56) | 28 (0.58) | 32 (0.64) | 26 (0.52) | 86 (0.58) |
| | C | 43 (0.44) | 20 (0.42) | 18 (0.36) | 24 (0.48) | 62 (0.42) |
| | NA | 2 | 2 | 0 | 0 | 0 |
| | | | p=0.859 0.91 (0.45–1.84) | p=0.382 0.72 (0.36–1.45) | p=0.727 1.18 (0.60–2.34) | p=0.793 0.92 (0.55–1.54) |
| IL-10 (-1082) rs1800896 | A | 38 (0.39) | 19 (0.38) | 16 (0.32) | 19 (0.38) | 54 (0.36) |
| | G | 60 (0.61) | 31 (0.62) | 34 (0.68) | 31 (0.62) | 96 (0.64) |
| | NA | 2 | 0 | 0 | 0 | 0 |
| | | | p=1 1.03 (0.51–2.08) | p=0.472 1.35 (0.65–2.76) | p=1 1.03 (0.51–2.08) | P=0.687 1.12 (0.67–1.90) |
| IL-17 (Exon 3/3'UTR) rs1974226 | C | 66 (0.67) | 42 (0.84) | 43 (0.86) | 39 (0.78) | 124 (0.83) |
| | A | 32 (0.33) | 8 (0.16) | 7 (0.14) | 11 (0.22) | 26 (0.17) |
| | NA | 2 | 0 | 0 | 0 | 0 |
| | | | p=0.033 0.39 (0.16–0.93) | p=0.018 0.34 (0.14–0.83) | p=0.188 0.58 (0.26–1.28) | p=0.006 0.43 (0.23–0.79) |
| IL-17 (Exon 3) rs763780 | A | 90 (0.92) | 50 (1) | 50 (1) | 48 (0.96) | 148 (0.99) |
| | G | 8 (0.8) | 0 | 0 | 2 (0.04) | 2 (0.01) |
| | NA | 2 | 0 | 0 | 0 | 0 |
| | | | p=0.051 | p=0.051 | p=0.495 0.47 (0.10–2.29) | p=0.0099 0.15 (0.03–0.73) |
| IL-18 (-137) rs187238 | G | 69 (0.70) | 41 (0.82) | 40 (0.8) | 38 (0.76) | 119 (0.79) |
| | T | 29 (0.30) | 9 (0.18) | 10 (0.2) | 12 (0.24) | 31 (0.21) |
| | NA | 2 | 0 | 0 | 0 | 0 |
| | | | p=0.164 0.52 (0.22–1.21) | p=0.241 0.59 (0.26–1.35) | p=0.561 0.75 (0.34–1.64) | p=0.129 0.62 (0.34–1.11) |
| IL-18 (-607) rs1946518 | A | 78 (0.8) | 45 (0.9) | 44 (0.88) | 46 (0.92) | 135 (0.9) |
| | C | 20 (0.2) | 5 (0.1) | 6 (0.12) | 4 (0.08) | 15 (0.1) |
| | NA | 2 | 0 | 0 | 0 | 0 |
| | | | p=0.163 0.43 (0.15–1.23) | p=0.257 0.53 (0.20–1.42) | p=0.061 0.34 (0.11–1.05) | p=0.025 0.43 (0.21–0.89) |

[a]Control vs. natural immunity. [b]Control vs. carrier. [c]Control vs. chronic hepatitis. arrier. [d]Control vs. all patients. NA: missing allele; F: frequency; OR: odds ratio; CI: confidence intervals.

**Table 2.** Genotype distribution, frequencies, and statistical analysis in the control and patient groups.

| Gene | Genotype | Control (n=50) (F) | Natural immunity (n=25) (F) p-value OR (95%CI)[a] | Carrier (n=25) (F) p-value OR (95%CI)[b] | Chronic hepatitis (n=25) (F) p-value OR (95%CI)[c] | All patients (n=75) (F) p-value OR (95%CI)[d] |
|---|---|---|---|---|---|---|
| TNF-α (-308) rs1800629 | GG | 45 (0.90) | 18 (0.72) p=0.091 3.5 (0.98–12.8) | 21 (0.84) p=0.728 1.71 (0.41–7.04) | 20 (0.8) p=0.286 2.25 (0.58–8.65) | 59 (0.79) p=0.142 2.44 (0.83–7.16) |
| | GA | 5 (0.10) | 6 (0.24) p=0.164 0.35 (0.10–1.29) | 3 (0.12) p=1 0.81 (0.18–3.72) | 5 (0.2) p=0.286 0.44 (0.11–1.70) | 14 (0.19) p=0.213 0.48 (0.16–1.44) |
| | AA | 0 | 1 (0.04) p=0.33 | 1 (0.04) p=0.333 | 0 p=1 | 2 (0.02) p=0.516 |
| | NA | 0 | 0 | 0 | 0 | 0 |
| IFN-γ (+874) rs2430561 | AA | 10 (0.20) | 5 (0.2) p=1.00 1 (0.3–3.3) | 6 (0.24) p=0.768 0.79 (0.25–2.5) | 7 (0.28) p=0.559 0.64 (0.21–1.96) | 18 (0.24) p=0.665 0.79(0.33–1.89) |
| | AT | 29 (0.58) | 15 (0.6) p=0.534 0.9 (0.34–2.44) | 14 (0.56) p=1 1.08 (0.41–2.86) | 12 (0.48) p=0.466 1.50 (0.57–3.93) | 41 (0.55) p=0.854 1.14 (0.56–2.36) |
| | TT | 11 (0.22) | 5 (0.2) p=0.547 1.13 (0.34–0.84) | 5 (0.2) p=0.547 1.13 (0.34–0.84) | 6 (0.24) p=1 0.89 (0.28–2.78) | 16 (0.21) p=1.00 1.04 (0.44–2.48) |
| | NA | 0 | 0 | 0 | 0 | 0 |
| IL-10 (-592) rs1800872 | AA | 6 (0.12) | 4 (0.17) p=4.720 0.70 (0.18–2.75) | 7 (0.28) p=0.113 0.36 (0.11–1.217) | 1 (0.04) p=0.411 3.35 (0.38–29.48) | 12 (0.16) p=0.610 0.72 (0.25–2.07) |
| | AC | 43 (0.88) | 20 (0.83) p=0.720 1.43 (0.36–5.65) | 18 (0.72) p=0.113 2.79 (0.82–9.45) | 24 (0.96) p=0.411 0.30 (0.03–2.63) | 62 (0.84) p=0.610 1.38 (0.48–3.98) |
| | CC | 0 | 0 p=1.00 | 0 p=1 | 0 p=1 | p=1 |
| | NA | 1 | 1 | 0 | 0 | 1 |
| IL-10 (-1082) rs1800896 | AA | 9 (0.18) | 5 (0.2) p=1 0.9 (0.25–3.04) | 2 (0.08) p=0.314 2.58 (0.51–13.02) | 3 (0.12) p=0.749 1.35 (0.33–5.46) | 10 (0.13) p=0.611 1.46 (0.54–3.91) |
| | AG | 20 (0.41) | 9 (0.36) p=0.802 1.23 (0.45–3.32) | 12 (0.48) p=0.624 0.75 (0.28–1.97) | 13 (0.52) p=0.460 0.64 (0.24–1.68) | 34 (0.46) p=0.712 0.83 (0.40–1.72) |
| | GG | 20 (0.41) | 11 (0.44) p=0.808 0.88 (0.33–2.32) | 11 (0.44) p=0.808 0.88 (0.33–2.32) | 9 (0.36) p=0.802 1.23 (0.45–3.32) | 31 (0.41) p=1 0.98 (0.47–2.03) |
| | NA | 1 | 0 | 0 | 0 | 0 |
| IL-17 (Exon 3/3'UTR) rs1974226 | CC | 26 (0.53) | 18 (0.72) p=0.14 0.44 (0.16–1.24) | 19 (0.76) p=0.078 0.36 (0.12–1.05) | 15 (0.6) p=0.627 0.75 (0.28–2.00) | 52 (0.69) p=0.087 0.50 (0.24–1.03) |
| | CA | 14 (0.29) | 6 (0.24) p=0.785 1.27 (0.42–3.83) | 5 (0.2) p=0.576 1.6 (0.50–5.10) | 9 (0.36) p=0.598 0.71 (0.25–1.98) | 20 (0.27) p=0.839 1.10 (0.49–2.46) |
| | AA | 9 (0.18) | 1 (0.04) p=0.149 5.4 (0.64–45.3) | 1 (0.04) p=0.149 5.4 (0.64–45.3) | 1 (0.04) p=0.149 5.4 (0.64–45.3) | 3 (0.04) p=0.031 4.40 (1.36–17.1) |
| | NA | 1 | 0 | 0 | 0 | |
| IL-17 (Exon 3) rs763780 | AA | 41 (0.84) | 25 (1) p=0.045 | 25 (1) p=0.045 | 23 (0.92) p=0.478 0.45 (0.09–2.28) | 73 (0.97) p=0.008 0.14 (0.03–0.69) |
| | AG | 8 (0.16) | 0 (0) p=0.045 | 0 (0) p=0.045 | 2 (0.08) p=0.478 0.45 (0.09–2.28) | 2 (0.03) p=0.008 7.12 (1.44–35.13) |
| | GG | 0 | 0 p=1 | 0 p=1 | 0 p=1 | p=1 |
| | NA | 1 | 0 | 0 | 0 | 0 |
| IL-18 (-137) rs187238 | GG | 25 (0.51) | 16 (0.64) p=0.330 0.59 (0.22–1.58) | 15 (0.6) p=0.622 0.69 (0.26–1.84) | 14 (0.56) p=0.807 0.82 (0.31–2.15) | 45 (0.60) p=0.358 0.69 (0.34–1.43) |
| | GT | 19 (0.39) | 9 (0.36) p=1 1.13 (0.41–3.06) | 10 (0.4) p=1 0.95 (0.35–2.54) | 10 (0.4) p=1 0.95 (0.35–2.54) | 29 (0.39) p=1.00 1.00 (0.48–2.10) |
| | TT | 5 (0.10) | 0 (0) p=0.160 | 0 (0) p=0.160 | 1 (0.04) p=0.428 2.73 (0.30–24.7) | 1 (0.01) p=0.0351 8.40 (0.95–74.3) |
| | NA | 1 | 0 | 0 | 0 | |
| IL-18(-607) rs1946518 | AA | 38 (0.78) | 22 (0.88) p=0.357 0.47 (0.12–1.87) | 22 (0.88) p=0.357 0.47 (0.12–1.87) | 22 (0.88) p=0.357 0.47 (0.12–1.87) | 66 (0.88) p=0.139 0.47 (0.18–1.24) |
| | AC | 2 (0.4) | 1 (0.04) P=1 1.02 (0.09–11.84) | 0 (0) p=0.546 | 2 (0.08) p=0.560 0.48 (0.06–3.70) | 3 (0.04) p=1.00 1.02 (0.16–6.34) |
| | CC | 9 (0.18) | 2 (0.08) p=0.314 2.58 (0.51–13.02) | 3 (0.12) p=0.532 1.65 (0.40–6.73) | 1 (0.04) p=0.149 5.4 (0.644–45.3) | 6 (0.08) p=0.097 2.58 (0.86–7.80) |
| | NA | 1 | 0 | 0 | 0 | 0 |

[a]Control vs. natural immunity. [b]Control vs. carrier. [c]Control vs. chronic hepatitis. [d]Control vs. all patients. NA: missing allele; F: frequency; OR: odds ratio; CI: confidence intervals.

chronic HBV infection as well as susceptibility to severe fibrosis and increased necro-inflammatory activity[20]. It is thought that gene variants affecting TNF-α expression may play a role in different clinical outcomes, such as elimination, resolution, or fibrosis in HBV infection.

In chronic hepatitis B patients, despite the increase in serum IL-17 levels, lower IL-17R expression levels and a weaker response to IL-17 were detected in vitro compared to the healthy control group[4,5]. This phenomenon may be due to the reduction in IL-17R expression depending on the negative effect of high levels of IL-17 on cells expressing IL-17R. In light of this information, we argue that IL-17 level and genetic polymorphisms affecting this level may be associated with the clinical consequences of HBV infection. In our research, a correlation was observed between susceptibility to HBV and IL-17 (Exon 3) AA genotype, IL-17 (Exon 3/3'UTR) C, and IL-17 (Exon 3) A alleles. Additionally, a correlation was observed between protection against HBV and IL-17 (Exon 3/3' UTR) A and IL-17 (Exon 3) G alleles. However, in our literature review to compare our results, we determined that minimal studies evaluate the relationship between IL-17 genetic polymorphisms and HBV. In contrast to our results, in two studies conducted in Iran and China, the IL-17 (Exon 3) SNP was found not to affect the clinical course of HBV[21,22]. Our results will form the basis for studies evaluating the effect of IL-17 polymorphisms on the clinical course of HBV.

IL-18 directly activates CD8+ T cells, which are central to viral clearance, and genetic variations can affect pro-IL-18 production, conferring susceptibility to viral hepatitis[23]. In our study, a correlation was observed between susceptibility to HBV with IL-18 (-607) A allele, while the IL-18 (-607) C allele and IL-18 (-137) CC genotype were associated with protection against HBV infection. There is only one study conducted in the Turkish population, and unlike our study, no association was found between HBV with 607/-137 genotypes and alleles[24]. In studies on IL-18, the roles of polymorphisms in the -607 and -137 regions are controversial. Some studies have associated genetic variations with lower transcriptional activity, lower IL-18 production from hepatic macrophages, and less inhibition of HBV replication, while other studies have associated protection from HBV[25]. However, during the antiviral response, IL-18, which is considered the determining factor in controlling the Th1/Th2 balance, may have effects that may change the individual disease risk[23].

The research is precious because there are minimal studies on this subject in the Turkish population. In addition, our study is the first to investigate polymorphisms in the IL-17 gene in Turkish people. However, the study had some potential limitations. First, all the data for this study were obtained from a single-center study and may not represent the entire target population. The second is the failure to evaluate cytokine levels. Overall, this study should be considered exploratory and should be validated in subsequent studies.

## CONCLUSION

This study demonstrated a correlation between susceptibility to HBV and IL-17 Exon 3/3'UTR C, IL-17 Exon 3 A, IL-18 (-607) A alleles, and IL-17 Exon 3 AA genotype, whereas IL-18 (-137) TT genotype, TNF-α-308 G, and A alleles were associated with protection against HBV. Genome-wide association studies are a practical approach to understanding how polymorphisms affect diseases. Polymorphisms might be potential targets for gene therapies in treating chronic HBV infection. Our findings will form the basis for studies on the immunopathogenesis and pharmacogenetics of HBV infection.

## AUTHORS' CONTRIBUTIONS

**ENT:** Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **FZA:** Conceptualization, Methodology, Validation, Visualization. **VC:** Formal Analysis, Investigation, Methodology, Validation. **GB:** Formal Analysis, Investigation, Methodology, Validation. **MYT:** Software, Validation, Visualization.

## REFERENCES


1. World Health Organization. Hepatitis B. Geneva: World Health Organization; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
2. Li M, Zhuo Y, Xu Y, Chen H, Cheng Z, Zhou L. Genetic association of interleukin-6 polymorphism (rs1800796) with chronic hepatitis B virus infection in Chinese Han population. Viral Immunol. 2021;34(4):267-72. https://doi.org/10.1089/vim.2020.0211
3. Smith AJ, Humphries SE. Cytokine and cytokine receptor gene polymorphisms and their functionality. Cytokine Growth Factor Rev. 2009;20(1):43-59. https://doi.org/10.1016/j.cytogfr.2008.11.006
4. Xie H, Zeng J, Yan X, Shen N, Zheng X, Luo H. Clinical significance and properties of IFN-γ+IL-17+ Th17 cells in liver injury associated with chronic hepatitis B virus infection. Digestion. 2022;103(6):438-50. https://doi.org/10.1159/000526924
5. Zhang JY, Zhang Z, Lin F, Zou ZS, Xu RN, Jin L, et al. Interleukin-17-producing CD4(+) T cells increase with severity of liver damage in

patients with chronic hepatitis B. Hepatology. 2010;51(1):81-91. https://doi.org/10.1002/hep.23273

6. Zheng MH, Qiu LX, Xin YN, Pan HF, Shi KQ, Chen YP. Tumor necrosis factor-alpha-308A allele may have a protective effect for chronic hepatitis B virus infection in Mongoloid populations. Int J Infect Dis. 2010;14(7):e580-5. https://doi.org/10.1016/j.ijid.2009.08.010
7. Park YK, Park ES, Kim DH, Ahn SH, Park SH, Lee AR, et al. Cleaved c-FLIP mediates the antiviral effect of TNF-α against hepatitis B virus by dysregulating hepatocyte nuclear factors. J Hepatol. 2016;64(2):268-77. https://doi.org/10.1016/j.jhep.2015.09.012
8. Wei Y, Zhao Z, Wang Z, Zhang K, Tang Z, Tao C. Relationships between IL-1β, TNF-α genetic polymorphisms and HBV infection: a meta-analytical study. Gene. 2021;791:145617. https://doi.org/10.1016/j.gene.2021.145617
9. Ablikim D, Zeng X, Xu C, Zhao M, Yang X, Feng X, et al. The multiple facets and disorders of B cell functions in hepatitis B virus infection. J Clin Med. 2023;12(5):2000. https://doi.org/10.3390/jcm12052000
10. Rybicka M, Woziwodzka A, Sznarkowska A, Romanowski T, Stalke P, Dręczewski M, et al. Genetic variation in IL-10 influences the progression of hepatitis B infection. Int J Infect Dis. 2020;96:260-5. https://doi.org/10.1016/j.ijid.2020.04.079
11. Romero R, Lavine JE. Cytokine inhibition of the hepatitis B virus core promoter. Hepatology. 1996;23(1):17-23. https://doi.org/10.1002/hep.510230103
12. Li L. Association between the interferon-γ+874T/A polymorphism and susceptibility to hepatitis B virus infection: a meta-analysis. J Int Med Res. 2020;48(8):300060520945511. https://doi.org/10.1177/0300060520945511
13. Yu Y, Qu J, Zhou C, You G. Relationship of genetic polymorphisms in CTLA-4 and IL-18 with viral hepatitis: evidence from a meta-analysis. Epidemiol Infect. 2019;147:e313. https://doi.org/10.1017/S0950268819001997
14. Özkan H. Epidemiology of chronic hepatitis B in Turkey. Euroasian J Hepatogastroenterol. 2018;8(1):73-4. https://doi.org/10.5005/jp-journals-10018-1264
15. VHSD. Turkey viral hepatitis diagnosis and treatment guide. Saglik Mah: VHSD; 2017. Avalaible from: https://www.vhsd.org/tr/article/desc/48317/tu-rkiye-viral-hepatitler-tani-ve-tedavi-kilavuzu-2-7.html#googtrans(tr|en)
16. Tunçbilek S. Relationship between cytokine gene polymorphisms and chronic hepatitis B virus infection. World J Gastroenterol. 2014;20(20):6226-35. https://doi.org/10.3748/wjg.v20.i20.6226
17. Börekçi G, Aras N, Kandemir Ö, Yalın S, Karakaş Çelik S, Berköz M. Investigation of the association between chronic hepatitis B and C infections and TNF-α (-308) gene polymorphism. Mikrobiyol Bul. 2016;50(2):236-44. https://doi.org/10.5578/mb.20953
18. Basturk B, Karasu Z, Kilic M, Ulukaya S, Boyacioglu S, Oral B. Association of TNF-alpha -308 polymorphism with the outcome of hepatitis B virus infection in Turkey. Infect Genet Evol. 2008;8(1):20-5. https://doi.org/10.1016/j.meegid.2007.09.001
19. Park YK, Lee JM, Kim DY, Chang HY, Kim JK, Lee CK, et al. Association between polymorphism of tumor necrosis factor-alpha promoter and response to lamivudine treatment in patients with chronic hepatitis B. Dig Dis Sci. 2010;55(7):2043-8. https://doi.org/10.1007/s10620-009-0983-1
20. Zhou F, Qiu LX, Cheng L, Wang MY, Li J, Sun MH, et al. Associations of genotypes and haplotypes of IL-17 with risk of gastric cancer in an eastern Chinese population. Oncotarget. 2016;7(50):82384-95. https://doi.org/10.18632/oncotarget.11616
21. Wang J, Liu Y, Xie L, Li S, Qin X. Association of IL-17A and IL-17F gene polymorphisms with chronic hepatitis B and hepatitis B virus-related liver cirrhosis in a Chinese population: a case-control study. Clin Res Hepatol Gastroenterol. 2016;40(3):288-96. https://doi.org/10.1016/j.clinre.2015.10.004
22. Gheshlaghi A, Haghshenas MR, Safarpour AR, Hosseini SY, Fattahi MR, Sarvari J. IL-17 genetic variations increase the risk of cirrhotic/hepatocellular carcinoma in patients with hepatitis B virus infection. Iran J Immunol. 2021;18(2):130-40. https://doi.org/10.22034/iji.2021.88020.1852
23. Yasuda K, Nakanishi K, Tsutsui H. Interleukin-18 in health and disease. Int J Mol Sci. 2019;20(3):649. https://doi.org/10.3390/ijms20030649
24. Hirankarn N, Manonom C, Tangkijvanich P, Poovorawan Y. Association of interleukin-18 gene polymorphism (-607A/A genotype) with susceptibility to chronic hepatitis B virus infection. Tissue Antigens. 2007;70(2):160-3. https://doi.org/10.1111/j.1399-0039.2007.00865.x
25. Amirpour-Rostami S, Kazemi Arababadi M. IL-18 and IL-1β gene polymorphisms: the plausible risk factors for chronic hepatitis B. Viral Immunol. 2019;32(5):208-13. https://doi.org/10.1089/vim.2018.0155