Int J Clin Exp Med 2025;18(1):1-8
www.ijcem.com /ISSN:1940-5901/IJCEM0157741

Original Article

Interaction analysis of genetic polymorphisms in Il12A and IL12B with hepatitis B virus infection in an Iranian population

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Received May 13, 2024; Accepted November 27, 2024; Epub January 15, 2025; Published January 30, 2025

Abstract: Objectives: This study aims to explore how IL12A and IL12B genotypes affect the development of chronic hepatitis B. Methods: A total of 360 patients, 390 healthy controls, and 212 healthy individuals who had recovered from HBV infection were included in the study. Polymorphisms at positions -1148T/C (rs2243123) and 277G/A (rs568408) in the Interleukin 12A (IL-12A) gene, as well as rs6887695G/C in the Interleukin 12B (IL-12B) gene, were analyzed using the polymerase chain reaction-restriction fragment length polymorphism method. Results: The frequencies of rs568408 genotypes in HBV patients were GG (68.5%), AG (28.2%), and AA (1.9%); in healthy controls they were GG (69%), AG (24.6%), and AA (3.7%); while in the healed group they were GG (75.1%), AG (25.1%), and AA (2.6%), with a *p*-value of 0.405. The frequencies of -1148TT, TC, and CC genotypes in the chronic HBV group were 72.3%, 24.9%, and 3.1%; in the healthy group they were 64.2%, 29.2%, and 5.9%; and in the cleared group they were 66%, 29.1%, and 6.8%, with a *p*-value of 0. 24. The frequencies of rs6887695 genotypes in HBV patients, healthy controls, and the cleared group for GG were 54.3%, 38.1%, and 8.9%, respectively; for GC they were 38.2%, 44.8%, and 43.5%, respectively; and for CC they were 8.4%, 8.6%, and 7.9%, respectively (P=0.314). Conclusions: This study is the first to investigate the role of genetic polymorphisms (rs2243123, rs2243123, and rs6887695) of IL12A and IL12B genes in the development of chronic hepatitis B in the Iranian population.

Keywords: Hepatitis B virus, single nucleotide polymorphism, interleukin-12A, chronic infection

Introduction

Hepatitis B infection is a liver inflammatory illness caused by HBV, affecting an estimated 500 million individuals globally, predominantly in Asia and Africa [1]. The complex interaction between viral and host factors contributes to the chronicity of HBV, with genetic factors within the host's immune system potentially playing a significant role. Recent genetic research suggests substantial variability in the location of these genes across different populations and families. Cytokines, a family of proteins that regulate immune responses, play a crucial role in defending against viral infections by influencing the immune response pattern and directly inhibiting viral replication [2-4].

Individuals exhibit varying capacities for cytokine production, which correlate with polymorphisms in cytokine gene promoters. These differences can be attributed to various molecular mechanisms such as transcription, translation, and secretion pathways. Interleukin-12 (IL-12) is a proinflammatory cytokine made up of a 35 kDa (Molecular weight) light chain and a 40 kDa heavy chain encoded by the IL12A and IL12B genes on different chromosomes. Initially identified as a natural killer-stimulating factor and cytotoxic lymphocyte maturation factor, IL-12 is essential for cell-mediated immunity and Th1 differentiation, promoting the development of interferon-γ- Th1 cells from naive T helper cells, also known as $CD4^+$ T cells. Cell-mediated immunity is believed to play a pivotal role in

https://doi.org/10.62347/MAJB4588

clearing viruses and determining disease progression during HBV infection [5].

Previous studies indicated that polymorphisms in IL-12A and IL-12B were associated with inflammatory, chronic diseases and cancer, such as hepatitis, psoriasis, Barrett's esophagus, asthma, arteritis, and cervical cancer [6-8]. Genetic differences can impact the outcomes of HBV infection in patients, with reports on human leukocyte antigen (HLA) genes and various cytokine genes linked to HBV susceptibility, persistence, or disease severity [9, 10]. There is limited research available specifically on the combination of SNPs in the IL12A and IL12B genes and their predictive value for virological response in individuals with HBV infection. However, some studies have suggested that certain genetic variations in immune response genes, including those involved in the IL-12 pathway, may influence the virological response to antiviral therapy in patients with chronic HBV infection [11-13].

Further research is needed to determine if specific combinations of SNPs in the IL12A and IL12B genes have a strong predictive value for virological response in individuals with HBV infection. It is important to consider multiple genetic and clinical factors when assessing virological response to treatment in patients with HBV, as individual genetic variations may have varying effects on treatment outcomes. There have been studies that have explored the relationship between certain single nucleotide polymorphisms (SNPs) in the IL12A and IL12B genes and the levels of viral load and type of HBV genotype in individuals with hepatitis B virus (HBV) infection [14]. One study found that certain SNPs in the IL12A gene were associated with higher levels of viral load in individuals with HBV infection. Specifically, the presence of the rs568408 SNP in the IL12A gene was associated with higher viral load levels in individuals infected with HBV [15]. Another study found that certain SNPs in the IL12B gene were associated with HBV genotype. Specifically, the presence of the rs3212227 SNP in the IL12B gene was associated with the presence of HBV genotype C in individuals with chronic HBV infection [16-18].

Overall, these studies suggest that specific SNPs in the IL12A and IL12B genes may play a role in determining the levels of viral load and the type of HBV genotype in individuals with HBV infection. Further research is needed to fully understand the mechanisms behind these relationships and their potential implications for the management and treatment of HBV infection. This study focuses on investigating the association between single nucleotide polymorphisms in IL12A (rs568408 and rs2243123) and IL12B (rs6887695) with chronic hepatitis B virus infection in the Iranian population, using genotyping analysis.

These SNPs have been selected based on their location within linkage disequilibrium blocks, which are regions of the genome where genetic variations are inherited together more frequently than expected by chance. By selecting SNPs within these blocks, we can capture a broader range of genetic variation that may be associated with HBV. This study focuses on investigating the association between single nucleotide polymorphisms in IL12A (rs568408 and rs2243123) and IL12B (rs6887695) with chronic hepatitis B virus infection in the Iranian population, using genotyping analysis. The study aims to explore how these genetic variations may contribute to persistent HBV infection. Additionally, HBV genotyping conducted using the restriction fragment length polymorphism (RFLP) method following polymerase chain reaction (PCR) was implemented.

Methods

Study participants

Our study enrolled 360 patients with chronic HBV infection. Diagnosis of chronic hepatitis B was based on HBsAg seropositivity, absence of core antigens of the hepatitis B virus (anti-HBs (antibodies, and presence of anti-core antibodies of the IgG type. These patients also exhibited elevated serum Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels with positive HBV DNA findings on repeat testing. Additionally, 212 healthy blood donors who had recovered from HBV infection were included as a comparison group. These individuals were positive for anti-HBs and anti-HBc IgG antibodies, and negative for anti-HCV and anti-HIV antibodies. Another 390 healthy controls (HBsAg-/HBV-DNA-/anti-HBc-) were also recruited. The study protocol was approved by the ethical committee at Tarbiat Modares University. Informed consent was signed and received from the patients.

Table 1. Comparation of demographic variables in the studied groups

Variables		Case (n=360)	Control (n=390)	Clear (n=212)	*p*-value
Age (yrs.)	Mean ± SD	(38.4 ± 9.54)	(39.2 ± 10.7)	(43.7 ± 12.5)	0.012
Sex	Male N (%)	179 (49.9)	182 (46.67)	129 (60.7)	0.031
	Female N (%)	181 (50.1)	208 (53.33)	83 (39.3)	

The inclusion criteria were as follows: (1) Patients with chronic HBV infection; (2) Diagnosis of chronic hepatitis B based on HBsAg seropositivity; (3) Absence of anti-HBs antibodies and presence of anti-core antibodies of the IgG type; (4) Patients exhibiting elevated serum ALT and AST levels; (5) Patients with positive HBV DNA findings on repeat testing. The exclusion criteria were as follows: (1) Patients with acute HBV infection; (2) Patients with other types of liver diseases; (3) Patients with co-infection of HIV or HCV; (4) Patients with positive anti-HBs antibodies.

HBV marker detection

Plasma samples from all participants were stored at -28°C. HBsAg screening was conducted using enzyme-linked immunosorbent assay (ELISA) from Behring, Germany. Anti-HBc screening was done through a manual microplate enzyme immunoassay with a commercial kit from RADIM, Italy, based on competitive enzyme immunoassay (EIA).

Genomic DNA extraction

Genomic DNA was extracted from peripheral blood leukocytes using standard salting-out extraction methods and stored at -20°C for future analysis.

Polymorphism analysis

Polymorphisms in the IL-12A and IL-12B genes were analyzed via polymerase chain reaction-restriction fragment length polymorphism assay (PCR-RFLP). Amplifications of specific gene fragments were performed with certain PCR conditions and thermal cycling parameters. After amplification, PCR products were visualized under UV light following agarose gel electrophoresis with ethidium bromide staining. Quality control was ensured by re-genotyping a subset of samples with commercial sequencing, showing high concordance between PCR-RFLP and sequencing results.

Statistical analysis

Chi-square tests were used to assess genotype distribution in a Hardy-Weinberg equilibrium. Differences in demographic characteristics and genotype distribution among HBV patients, healthy controls, and those with clearance were analyzed using t-tests, Mann-Whitney U tests, and chi-square tests. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and all statistical analyses were performed using SPSS version 21 with a significance level set at $P < 0.05$.

Results

We conducted comparisons between cases of persistent HBV infection, healthy controls, and individuals who cleared HBV infection. Specifically, we examined the relationship between IL12A (rs6887695G/C, rs568408G/A) and IL12B (rs2243123T/C) polymorphisms with susceptibility to persistent HBV infection. Details of the 360 persistent HBV infection cases, 390 healthy controls, and 212 individuals who healed HBV infection, are provided in **Table 1**. The mean age of patients, controls, and individuals in the clearance group was 38.4 ± 9.54, 39.2 ± 10.7, and 43.7 ± 12.6, respectively, with a significant difference in age across the groups (**Table 1**).

Females accounted for 53.1% of the control group with 46.9% being male, whereas in the patient group, 50.1% were females and 49.9% were males. The clearance group consisted of 39.3% females and 60.7% males, leading to significant differences in gender distribution. Age and gender were controlled for using multinomial logistic analysis (**Table 2**). Furthermore, analysis of socio-economic factors revealed no significant differences between patient and control groups. The genotype distributions of IL12A rs568408, rs6887695, and IL12B rs2243123 in cases, controls, and the HBV infection clearance group can be found in **Table 2**.

Table 2. Distribution of genotypes of IL12A and IL12B and their associations with risk of *chronic hepatitis B virus infection*

Variables	Cases N (%)	Control N (%)	*P*-value	OR (95% CI)
Age	(38.4 ± 9.54)	(39.2 ± 10.7)	0.21	1.00 (0.99-1.01)
Sex				
Male	179 (49.9)	182 (46.6)	0.91	0.91 (0.677-1.22)
Female*	181 (50.1)	207 (53.1)	-	Reference level
IL12A rs568408				
GG*	268 (70.5)	238 (70)	-	Reference level
AG	106 (27.9)	90 (26.5)	0.91	0.98 (0.701-1.373)
AA	6 (1.6)	12 (3.5)	0.07	0.40 (0.148-1.107)
G*	650 (85.5)	576 (84.7)	-	-
A	110 (14.5)	104 (15.3)	0.830	
IL12A rs2243123				
TT*	272 (71.6)	221 (65)	-	Reference level
TC	97 (25.5)	98 (28.8)	0.054	0.736 (0.539-1.005)
CC	11 (2.9)	21 (6.2)	0.77	0.922 (0.532-1.597)
T*	640 (84.2)	542 (79.7)	-	Reference level
C	120 (15.8)	138 (20.3)	0.043	
IL12B rs6887695				
GG*	203 (53.9)	158 (46.5)	-	Reference level
GC	144 (37.4)	154 (45.3)	0.12	0.765 (0.546-1.072)
CC	33 (8.7)	28 (8.2)	0.028	0.425 (0.198-0.913)
G*	206 (27.1)	458 (67.4)	-	Reference level
C	554 (72.9)	222 (32.6)	0.035	

*Reference level.

Table 3. Association of SNPs of IL12A and IL12B genotypes in the studied groups both in autosomal dominant and recessive models

Genotypes	SNPs	Dominant	Recessive
		Case vs Control	*Case vs Control*
IL12A	rs568408	OR: 4.9656	OR: 6.0854
	rs2243123	CI: 3.2128-7.6747	CI: 2.7211-13.6094
		P < 0.0001	P < 0.0001
IL12B	rs6887695	3.6410	3.2285
		2.4063-5.5092	1.7101-6.0951
		P < 0.0001	P < 0.0003

IL, interleukin; vs, versus; OR, odds ratio; CI, confidence interval; *p*, *p*-value.

Table 3 shows the risk of carriage of the minor allele for case and control groups in both autosomal dominant and recessive modes of inheritance. The risk of carriage of the minor allele of IL12A rs568408 was significantly higher in the case group when compared with the moderate group in both models of inheritance (dominant OR: 4.9656, CI: 3.2128-7.6747, P < 0.0001; recessive OR: 6.0854, CI: 2.7211-3.6094, P < 0.0001).

After analyzing the genotypes of healthy and patients subjects with the SNP Analyzer software, 4 haplotypes were displayed as results. Among these 4 haplotypes, haplotype H2 with CG sequence and frequency of 37.34% was the most common haplotype and the rarest haplotype was H6 with CC sequence and frequency of 5.47% (**Table 4**).

Discussion

In this study, we sought to investigate the interaction between genetic variations in IL12A and IL12B genes with chronic hepatitis B (HBV) infection. Our findings shed light on the potential roles of these genetic variations in the susceptibility to HBV infection in the Iranian population. IL-12 is a cytokine with both pro-inflammatory and anti-inflammatory properties that plays a crucial role in the clearance of HBV in vivo. The clearance of HBV and seroconversion in chronic carriers following IFN treatment relies on a signifi-

Table 4. Haplotypes of polymorphisms rs568408, rs2243123, and their relationship with CHB

Genotypes	Haplotype	Percent (%)	Sequence	OR (CI)	*p*-value
IL12A (rs568408, rs2243123)	H1	17.1	AG	0.638 (0.163-1.25)	0.081
	H2	37.34	CG	1.816 (1.037-3.41)	0.006
	H3	14.82	CT	1.314 (0.467-3.29)	0.13
	H4	18.60	GT	0.524 (0.27-0.967)	0.032

cant increase in IL-12 production. Patients with chronic HBV infection show lower levels of IL-12 compared to healthy individuals, suggesting a potential inhibitory effect on HBV replication. Concentrations of IL-12 reflect the current status of the immune system, while genotypes remain unaffected by internal or external signals [19-21]. Genetic variations in the IL-12 gene may impact protein expression, leading to immune system disorders, autoimmune diseases, and potential malignancies [22].

The rs568408 polymorphism, located in the 3'-untranslated region, can influence protein translation levels and has been associated with modulating IL-12 levels, particularly in Asian populations. This polymorphism may affect the immune response to HBV antigens [23-26]. Studies suggest that SNP rs568408 (G/A) could influence HBV infection and immune evasion by disrupting IL-12 mRNA splicing or secretion. This genetic variation may contribute to hepatocellular carcinoma risk associated with HBV infection. Several molecular epidemiological studies have indicated an increased risk of various cancers with specific IL-12A genotypes, including cervical cancer, esophageal cancer, hepatocellular carcinoma, colorectal cancer, and osteosarcoma [8].

The rs2243123T/C gene, located in intron 1 of IL12A, is linked to inflammatory responses and has been associated with risks in various cancers. Genetic variations in inflammatory or apoptosis pathways may influence the risk of neuroendocrine tumors. Additionally, findings suggest associations with primary biliary cirrhosis, skin test reactivity to cockroaches, and IgE levels; particularly under a recessive genetic model [24, 27-30].

The rs6887695G/C polymorphism, located 60 kilobases upstream from the coding region in the IL12B gene, has shown associations with ulcerative colitis in different populations. In German and Japanese populations, specific SNPs, including rs6887695, have been linked to ulcerative colitis risk. Our study focused on exploring the potential role of three functional SNPs in IL-12A and IL-12B in chronic HBV infection susceptibility in an Iranian population. After analyzing 340 patients, 340 healthy individuals, and 123 HBV-cleared patients, matched for sex and age, we found that rs568408, rs2243123, and rs6887695 were not significantly associated with chronic HBV infection susceptibility [31].

Non-coding variants, such as those found in regulatory regions or intronic regions of genes, can still have important functional implications despite not directly affecting the protein sequence of the gene product. These non-coding variants can influence gene expression, splicing patterns, RNA stability, and protein synthesis, all of which can ultimately impact the course of infection and response to treatment in individuals with HBV. Gene Expression Regulation: Non-coding variants in regulatory regions, such as promoters or enhancers, can alter the binding of transcription factors or other regulatory proteins, leading to changes in gene expression levels. For example, a non-coding variant near the IL12A or IL12B gene may affect the expression of these cytokines, which play crucial roles in immune response pathways against HBV. Splicing Alterations: Intronic non-coding variants can disrupt normal splicing patterns, leading to the production of aberrant mRNA isoforms. These alternative splice variants may encode proteins with altered functions or stability, impacting the immune response to HBV infection or the efficacy of antiviral treatments. RNA Stability and Translation Efficiency: Non-coding variants can also affect RNA stability or translation efficiency, influencing the abundance of cytokine transcripts or the production of functional cytokines. Variants that alter RNA secondary structures or microRNA binding sites can modulate the availability of key immune response molecules during HBV infection. Epigenetic Modifications: Non-coding variants can influ-

ence epigenetic modifications, such as DNA methylation or histone acetylation, which regulate gene expression patterns. Changes in epigenetic marks near the IL12A and IL12B genes can impact their transcriptional activity and ultimately affect the immune response to HBV [32]. By modulating these molecular mechanisms, non-coding variants can indirectly impact the host immune response, viral replication, liver inflammation, and overall disease progression in individuals with chronic hepatitis B. Understanding the functional consequences of non-coding variants in the context of HBV infection can provide insights into the underlying mechanisms of disease pathogenesis and inform personalized treatment strategies tailored to the individual's genetic profile.

Conclusion

One of the most influential factors in the improvement or persistence of infectious and non-infectious diseases such as autoimmune, chronic, and inflammatory diseases involve genetic factors of the individual's immune system. Polymorphisms are indicators of these genetic factors. The profile of SNP variations in genes encoding immune system pathways, plays a predictive role in susceptibility, recovery, or chronicity of infectious or non-infectious diseases in clinical medicine. These polymorphisms are influenced in different ethnicities and populations. Due to the location of the polymorphism (rs568408) in the untranslated region, which acts as a miRNA binding site, although only miRNA (202/202-3P) has been identified to bind to rs568408G/A and does not affect the transcription of IL12A, this region still affects the stability of mRNA and ultimately the translation of interleukin-12. Assuming that the production of interleukin-12 initiates an effective innate immune response against viral infections, as mentioned before, this SNP is associated with the progression of inflammatory, autoimmune, chronic, and cancerous diseases. We investigated the association of this polymorphism with the susceptibility to chronic hepatitis B in Iranian patients and, based on the results, we did not observe any significant differences between the genotypes and alleles of patients with chronic hepatitis B and healthy individuals. Therefore, the existence of this polymorphism may not serve as a predictor in the persistence of chronic hepatitis B.

Acknowledgements

The authors thank all patients and participants for their valuable cooperation in this study.

Disclosure of conflict of interest

None.

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