Iran J Public Health, Vol. 53, No.11, Nov 2024, pp.2440-2450

Review article

Host Genetic Variations and their Implications on HBV and HCV Infection in the Iranian Population: A Comprehensive Systematic Review

*Asma Khorshid Shamshiri [1], Forouzan Amerizadeh [2,3], Zahra Nasrpour Navaei [1], *Alireza Pasdar [1,4]*

1. *Department of Medical Genetics and Molecular Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
2. *Department of Neurology, Mashhad University of Medical Sciences, Mashhad, Iran*
3. *Internal Medicine Department, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
4. *Division of Applied Medicine, Medical School, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK*

***Corresponding Author:** Email: pasdara@mums.ac.ir

The first two authors contributed equally to the study

(Received 19 Feb 2024; accepted 22 Apr 2024)

Abstract

Background: Background: Hepatitis virus infections are among the serious emerging health issues. They are the primary causes of cirrhosis and hepatocellular carcinoma. Growing evidence shows a link between certain genomic variations and inflammation including viral infection such as HBV and HCV. Therefore, this study aimed to comprehensively review studies that analyze the effect of host genomic variations on the risk of contracting viral hepatitis in Iranian population.

Methods: The study was conducted according to the PRISMA Statement. All Persian and English case-control articles published until the beginning of June 2023 were included in the study. Two authors reviewed the articles independently. The third author reviewed the final results. Pathway analysis and protein interactions were also performed using GO and STRING databases.

Results: Seventy relevant studies were retrieved. Fifty-three studies examined the association of SNPs with the risk of HBV infection. In terms of genetic variations, 25 genes and 44 SNPs were identified. Tumor necrosis factor alpha, Interleukin 28B, and Interleukin 10 were the most prevalent considered genes. The most common polymorphisms were in the interleukin family. Moreover, the top five identified molecular functions were cytokine activity, cytokine receptor binding, molecular function regulator, protein binding, and signaling receptor binding.

Conclusion: The polymorphisms of genes involved in the production of immune factors, cytokines, interleukins, and their receptors are associated with the risk of HBV and HCV infections in the Iranian population. Moreover, the extracellular and intracellular signaling pathways and the regulating molecules of these processes can be considered as important factors in liability for these viral infections.

Keywords: Hepatitis virus; Genetic variation; Polymorphism

Introduction

Hepatitis C (HCV) and B virus (HBV) infections are two serious, emerging health issues. HBV infects almost two billion individuals, whereas HCV infects 210 million subjects worldwide (1). The primary causes of hepatocellular carcinoma (HCC), liver cirrhosis (LC), and chronic hepatitis (CH) are considered as outcome of these two viral diseases. About 78% of HCC cases are related to HBV or HCV, and HCC is the third most common cancer mortality cause worldwide (2). The genetic background of people with a viral infection affects the recovery or complications. In addition, identifying genetic susceptibility to this infection, may also help to better understand the mechanism of the host's response to the viral infections, resulting better management of hepatitis B and C patients (3).

Additionally, variations in the related genes influence the inflammation-causing factors directly. Single nucleotide polymorphisms (SNPs) are the most common genetic variations, which may impact the degree of inflammatory factor production and the strength of their reaction. Growing evidence shows a link between certain SNPs and inflammation of the liver such as chronic hepatitis, liver cirrhosis, and HCC (4, 5). Interferon (IFN), Interleukin (IL), tumor necrosis factor (TNF), and transforming growth factor (TGF) genes make up the majority of the genes. Previous research on liver cirrhosis has suggested numerous gene variants related to immune variables; however, the findings were inconsistent. Detection of genetic risk factors for liver cirrhosis might clarify the intricate nature of the illness and strengthen the evidence based treatments or proactive measures (4).

So far, scattered studies have been conducted in Iran on identifying genetic variants and hepatitis B and C. To our knowledge, there has not been a systematic review to assess polymorphism data on the infection of HBV and HCV in the Iranian population. Therefore, this study aimed to comprehensively review of studies that analyze host genetic variations and the risk of contracting hepatitis viruses.

Methods

Identification and selection of studies

Identifying genetic polymorphisms associated with hepatitis B and C virus infection in the Iranian population was the main objective of this study. To access related articles, the MeSH terms were searched in the three main international databases of Web of Science, Scopus, and PubMed, as well as the Iranian SID database. All Persian and English case-control articles published until the beginning of June 2023 were included in the study. Review, systematic review and meta-analysis, animal and/or in vitro studies, editorials, and letters to the editor were excluded.

Data extraction and quality control

The PRISMA statement was taken into consideration in writing this article (6). All articles were sorted by year of publication and then divided into two separate files. On the other hand, we conducted the Newcastle-Ottawa Scale (NOS) for all our case-control studies. Two authors (F. A. and Z. NN.) independently reviewed each file. A third author (A. KS.) resolved discrepancies by reading each file. Extracted data include authors, year, location, type of hepatitis virus, diagnostic and genotyping methods, sample size, demographic characteristics (age, sex), gene, SNP, genotype, allele frequencies, and case-control matching methods.

Statistical analysis

In the control group, the X^2 statistics was used to evaluate the allele frequencies for Hardy-Weinberg equilibrium testing. The analysis of GO function has been implemented to categorize the selected genes into three independent categories, namely biological process, cellular component, and molecular function. In the results of this database, the significance level for the FDR

scale was less than 5%, and the lowest value was considered the most relevant cellular pathway or function. In order to better understand the interactions between potential genes that were obtained from databases, the "Search Tool for the Retrieval of Interacting Genes/Proteins" (STRING; ver. 12.0; http://string db.org/) was employed to create a protein-protein interaction (PPI) network. This network represents the interactions between the proteins encoded by the potential genes we identified earlier. In the PPI network, each node represents a protein, and the edges between them represent their interactions. A node with many connections is known as a hub node, as it is a central point of the network with many interactions. Power of the studies was also calculated online (www.clincalc.com) according to each study's sample size of case and control groups.

Results

Study identification

The initial search with the mentioned terms identified 1160 (PubMed=148, Scopus=786, Web of science=226) articles. After removing the duplicate articles, the title and abstract of the remaining 1121 studies were reviewed for the primary detection of unrelated and relevant articles. At this stage, 981 studies were excluded, and the full texts of 140 articles were received and reviewed to confirm their relevance to the current systematic topic. Finally, 70 case-control studies evaluating the association of one or more polymorphisms with hepatitis B and C virus infection were included in the analysis (Fig. 1).

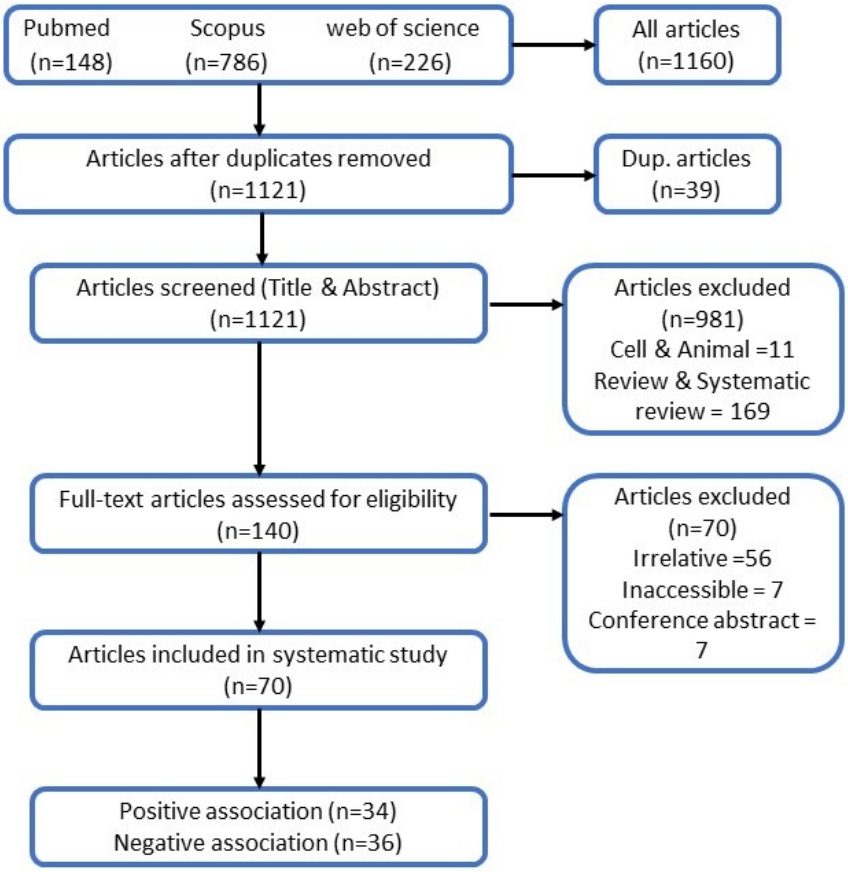

Fig. 1: Diagram of the systematic review process

On the other hand, we assessed the power of each study with positive associations. Among all studies, just nine (7-15) had a power of more than 80% (Table 1). Furthermore, regarding quality control, only four studies (8-10, 16) had a grade of 5 or 6 and good quality (Table S1), In contrast, other studies have a score of 4 or less, indicating their results' lack of reliability.

Data extraction

The selected studies included 11789 infected subjects and 11406 healthy controls (Table S1). The central part of Iran had the largest number of samples. Most studies (n=53) investigated the association of genetic polymorphisms with the risk of HBV infection, and seventeen studies included 3311 patients with the HCV virus and 2407 controls. The mean age was 28–61 in total subjects. Patients with HCV were mostly in their fourth decade of life. The case-control studies indicated a considerably varied sample size (ranging from 50 to 1063 individuals).

Evaluation of methodology indicated that most studies had used ELISA, RT-PCR, or a combination of these methods to diagnose patients. However, seven articles did not report the diagnostic procedure. Moreover, seven other articles had just reported diagnosis by medical records. The variation detection method was PCR-based, including PCR-RFLP, ARMS-PCR, SSP-PCR (Single Specific Primer-PCR), and TaqMan. In the matching process, confounding factors, including age and gender, were also considered.

Investigating genetic variations, 25 genes and 44 polymorphisms were identified to be assessed in the Iranian population in association with HBV or HCV infection. Tumor necrosis factor alpha (TNF-α; rs1800629) (9, 10), Interleukin 28B (IL-28B; rs12979860) (17, 18), and Interleukin 10 (IL-10; rs1800896) (19, 20) were the most prevalent considered genes. The most common polymorphisms were in the interleukin family. IL-10 and IL-16 genes had three related genetic variations, and other interleukin genes included 6, 12, 13, 17, 18, and 28 (Table 1).

Table 1: Distribution of genotypes and alleles investigated in association with the hepatitis B and C virus infection in Iran

Study Year	*Gene name*	*Polymorphism*	*Risky allele*	*Genotype frequency*						*Allele frequency*				*HWE**	*Power[d]*
				Cases			Controls			Cases (%)		Controls (%)			
				11[a]	12[b]	22[c]	11	12	22	1	2	1	2		
Alizadeh (2006) (37)	*CD14*	*rs2569190*	T	39	22	19	16	94	16	62.5	37.5	50.0	50.0	0.000	0.369
Alizadeh (2006) (38)	*CTLA-4*	*rs5742909*	T	41	10	0	13	10	6	90.2	9.8	92.7	7.3	0.000	0.057
							4								
Sepahi (2017) (39)		*rs4553808*	G	5	57	5	23	38	4	50.0	50.0	66.6	35.4	0.080	0.412
Khanizadeh (2012) (40)	*IFNGR1*	-611 A/G	G	82	11	3	76	11	17	69.7	30.3	67.2	32.8	0.010	0.063
					5			7							
		-56 T/C	C	74	86	40	42	10	55	58.5	41.5	46.7	53.3	0.888	0.620
								3							
Nasiri Ahmadabadi (2012) (7)	*IL-10*	*rs1800872*	A	31	24	2	22	55	23	75.4	24.6	49.5	50.5	0.721	0.869
Mirfakhar (2018) (41)		*rs1800871*	T	48	62	12	80	45	13	64.8	35.2	74.3	25.7	0.227	0.334
Sepahi (2014) (20)		*rs1800896*	G	15	20	15	6	39	5	50.0	50.0	51.0	49.0	0.00039	0.031
Moudi (2016) (19)				72	11	31	10	84	16	59.3	40.7	71.0	29.0	0.961	0.675
					8		0								
Romani (2014) (42)	*IL-16*	*rs4072111*	T	18	58	6	31	74	4	85.7	14.3	89.6	10.4	0.990	0.279
				1			6								
		rs11556218	G	43	14	55	12	21	55	47.6	52.4	58.8	41.2	0.044	0.766
					7		4	5							
Behelgardi (2015) (33)		*rs1131445*	C	11	12	20	13	10	27	68.3	31.7	70.6	29.4	0.536	0.070
				6	6		8	4							
Mousavi Nasab (2015) (18)	*IFNL3 / IL-28B*	*rs12979860*	T	57	74	16	37	34	9	63.9	36.1	67.5	32.5	0.961	0.058
Koolivand (2020) (17)				40	52	28	60	39	21	55.0	45.0	66.3	33.7	0.011	0.381

Table 1: Continued….

Larijani (2016) (43)	*IL-28B*	*rs8099917*	G	53	33	7	43	13	1	74.7	25.3	86.8	13.2	0.999	0.337
Attar (2016) (8)	*IL-6*	*rs1800795*	C	181	102	14	175	146	47	67.4	32.6	78.1	21.9	0.175	0.852
Azar (2016) (9)	*TNF-a*	*rs1800629*	A	114	215	80	228	233	22	54.2	45.8	71.3	28.7	0.00042	0.999
Heidari (2016) (10)				92	6	2	64	29	7	95.0	5.0	78.5	21.5	0.371	0.905
		-857 C/T	T	80	12	8	72	7	21	86.0	14.0	75.5	24.5	0.000	0.398
		-863 A/C	C	44	44	12	61	34	5	66.0	34.0	78.0	22.0	0.996	0.409
Larijani (2016) (44)		*rs1799724*	A	70	18	1	35	40	1	88.8	11.2	72.4	27.6	0.022	0.701
Ghavami (2018) (45)		*rs1799964*	C	176	78	4	161	108	8	83.3	16.7	77.6	22.4	0.127	0.398
Abdolmohammadi (2016) (11)	*CCR5*	CCR5Δ32 (rs333)	Del	352	5	0	397	51	7	99.3	0.7	92.8	7.2	0.004	0.996
Moudi (2019) (14)		*rs1799987*	A	22	36	42	40	39	21	60.0	40.0	40.5	59.5	0.162	0.818
Moudi (2016) (46)	*MIF*	*rs755622*	C	130	67	24	132	62	6	74.0	26.0	81.5	18.5	0.924	0.406
Eskandari (2017) (47)	*HLA-G*	14-bp Ins/Del	Del	90	104	5	53	144	0	71.4	28.6	63.5	36.5	0.00	0.348
Eskandari (2017) (28)	*TGF-β1*	*rs1800472*	T	130	39	0	147	16	0	89.0	11.0	95.0	5.0	0.805	0.446
		rs1800470	T	55	118	23	49	103	46	58.0	42.0	51.0	49.0	0.849	0.220
Fatemipour (2017) (12)	*STAT3*	*rs1053004*	T	18	5	10	4	14	32	62.1	37.9	22.0	78.0	0.428	0.943
Fattahi (2018) (48)	*CYP2E1*	*rs4646421*	T	33	14	7	61	25	3	74.0	26.0	82.0	17.0	0.976	0.157
Moudi (2018) (49)	*LAMC1*	*rs20558*	C	33	45	22	51	42	7	55.5	44.5	72.0	28.0	0.917	0.627
		rs20563	G	33	45	22	51	42	7	55.5	44.5	72.0	28.0	0.917	0.627
		rs10911193	T	44	44	12	61	34	5	66.0	34.0	78.0	22.0	0.996	0.409
Moudi (2019) (13)	*BIRC5*	*rs3764383*	G	42	41	17	82	54	4	62.5	37.5	77.9	22.1	0.373	0.606
		rs8073069	G	54	40	6	41	57	42	74.0	26.0	49.6	50.4	0.089	0.932
		rs9904341	C	31	47	22	74	59	7	54.5	45.5	73.9	26.1	0.544	0.779
		rs17878467	T	26	51	23	65	59	16	51.5	48.5	67.5	32.5	0.897	0.581
Ayatollahi (2019) (50)	*IL-12*	*rs568408*	A	105	35	8	37	34	9	82.8	17.2	95.2	4.8	0.961	0.725
Khanizadeh (2019) (15)	*miRNA-146a*	*rs2910164*	G	42	52	172	94	74	98	25.6	74.4	49.2	50.8	0.00	1.000
Moudi (2019) (14)	*VDR*	rs731236	C	33	45	22	51	42	7	55.5	44.5	72.0	28.0	0.917	0.627
		rs7975232	C	33	45	22	51	42	7	55.5	44.5	72.0	28.0	0.917	0.627
	MCP1	rs1024611	G	35	46	19	53	40	7	58.0	42.0	73.0	27.0	0.989	0.549
Zangi (2019) (51)	*IL-13*	*110 A/G (rs20541)*	A	106	170	26	135	130	18	63.2	36.7	70.6	39.3	0.191	0.441
Heidari (2020) (52)	*INFG*	*rs2430561*	A	35	108	78	48	109	43	51.2	48.8	40.3	59.7	0.439	0.573
Bahrami (2020) (53)	*VDR*	*rs2228570*	T	33	49	18	24	41	35	44.5	55.5	57.5	42.5	0.236	0.396
Sarrafnia (2020) (54)	*IL-18*	*rs360719*	G	64	53	3	51	50	19	75.4	24.6	62.9	37.1	0.530	0.499
Tayefinasrabadi (2020) (55)	*IL-17A*	*rs10484879*	A	110	54	8	109	73	17	78.4	21.6	77.6	22.4	0.641	0.029

Abbreviations. *CD14*: cluster of differentiation 14; *CTLA-4*: Cytotoxic T-Lymphocyte Associated Protein 4; *IFNGR1*: Interferon Gamma Receptor 1; *IL*: Interleukin; *IFNL3*: Interferon Lambda 3; *TNF- a*: Tumor necrosis factor alpha; *HLA*: human leucocyte antigen; *CCR5*: C-C Motif Chemokine Receptor 5; *MIF*: Macrophage Migration Inhibitory Factor; *TGF-β1*: transforming growth factor-beta; *STAT3*: Signal transducer and activator of transcription 3; *CYP2E1*: Cytochrome P450 2E1; *LAMC1*: Laminin Subunit Gamma 1; *BIRC5*: Baculoviral IAP repeat containing 5; *VDR*: Vitamin D Receptor; *MCP1*: monocyte chemoattractant protein 1; *INFG*: Interferon Gamma;

*The P-value of Hardy-Weinberg in controls

[a] Wild type genotypes

[b] Heterozygote genotype

[C] Mutant homozygote genotype

[d] The power of studies was calculated with SigmaPlot software version 14.0. (Alpha=0.050)

Moreover, the top five identified molecular functions were cytokine activity (TGFB1, CCL2, TNF, IFNG, MIF, IFNL3, IL6/10/13/16/17A/18), cytokine receptor binding (TGFB1, CCL2, STAT3, TNF, IFNG, MIF, IL6/10/13/18), molecular function regulator (IFNL3, MIF, VDR, IFNG, TNF, CCL2, STAT3, TGFB1, BIRC5,

IL6/10/13/16/17A/18), protein binding (CYP2E1, IFNL3, IFNGR1, IL12RB1, HLA-G, IFNG, TNF, MIF, CCR5, CCL2, STAT3, TGFB1, VDR, BIRC5, IL6/10/13/16/17A/18), and signaling receptor binding (IFNL3, HLA-G, IFNG, TNF, MIF, CCL2, STAT3, TGFB1, VDR, IL6/10/13/16/17A/18). Moreover, the biological pathways of negative regulation of primary miRNA processing (STAT3 and IL6), regulation of chronic inflammatory response to antigenic stimulus (IL10 and TNF), and chronic inflammatory response to antigenic stimulus (IL10 and TNF) were ranked first to third in the list, respectively. On the other hand, the position of CCR5, IL12RB1, IL17A/13, CD14, CTLA4, TNF, and HLA-G gene products are on the external side of the plasma membrane. Protein interactions are shown in Fig. 2.

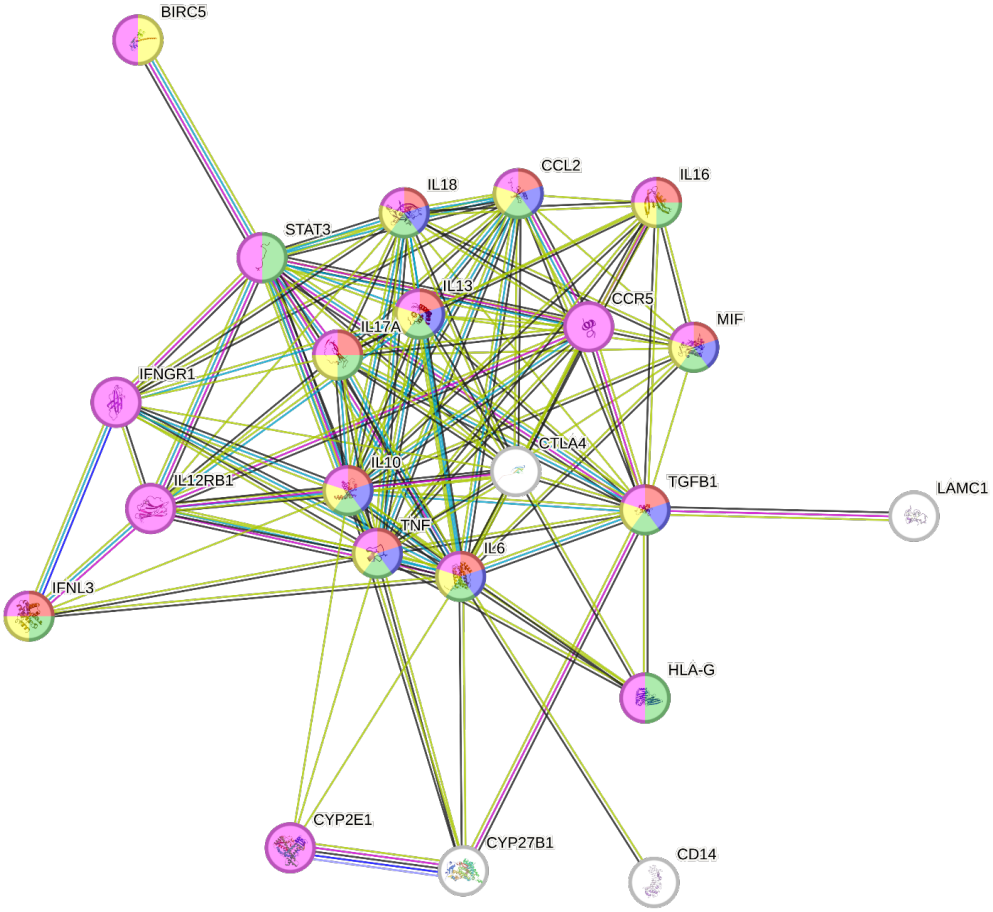

Fig. 2: Interaction between the proteins of the genes associated with HBV and HCV infections. Red: Cytokine activity, Pink: Protein binding, Blue: Cytokine receptor binding, Green: Signaling receptor binding, Yellow: Molecular function regulator activity.

Discussion

The role of genetic background in the contracting viral infections has been proven (21). According to WHO, HBV and HCV infections are spread worldwide and can cause liver problems (22). Several pathways are involved in the pathogenesis of hepatitis B and C infection, with emerging data on dissecting the genetic basis of the disease. The role of cytokines and immune system factors, including interleukin-6, 10, 12, 27, membrane cofactor CD46 protein, tumor necrosis factor-alpha, and interferon-gamma, has been documented in the development of viral infection

(23). Based on Genome-Wide Association Studies (GWAS) or functional analysis, new players such as AAMDC, HLA alleles, interferon-alpha, and proteins involved in glucose metabolism have also been suggested (24, 25). Nevertheless, it is crucial to replicate and validate these findings in diverse populations to ensure their reliability and accuracy. In this context, we will briefly address some points of our findings as follows:

Cytokines, which are small proteins, play a critical role in regulating the growth and functioning of various cells in the immune system and blood. When they are released, they act as signals to prompt the immune system. Cytokines have an impact on the growth of all blood cells and other cells that contribute to the body's immune response and ability to modulate inflammation. Overall, 25 patients with chronic HBV and HCV co-infection were collected, and the TGFβ1, CCL2, and IFNG serum levels were measured. The patients had high levels of TGFB and CCL2 after four weeks and decreased levels of IFNG compared with the baseline (26). Numerous studies have examined the variations in genes associated with this pathway. For example, an association was demonstrated between the TGFβ1 -509C>T polymorphism and an increased susceptibility to chronic hepatitis C. This polymorphism leads to elevated TGFβ1 levels, which subsequently hinder the production of IFN-γ, thereby contributing to the progression of cirrhosis (27). Although this variant was not associated with the risk of contracting hepatitis B in a study, two other variants of TGFβ1, rs1800470 and rs1800472, were associated with the risk of infection with HBV (28). Moreover, TGFβ1 rs1800471 could be a host genetic factor associated with susceptibility to HCV infection (29). Heterozygosity for CCR5Δ32 was linked to increased susceptibility to HBV-related liver disease, while VDR a/a and TNF-β A/A were associated with disease severity. Additionally, the VDR a/a allele was found to be correlated with higher viral load (30). On the other hand, CCR5Δ32 has a protective effect in resistance to HBV infection in the Iranian population. The heterozygosity for CCR5/ CCR5Δ32 (W/D) in healthy controls was greater than in cases (11.2% vs 2%) (11). Furthermore, another Iranian study indicated significant associations with susceptibility to chronic HBV infection in association with CCR5-2459A/G, VDR-APa1A/C, and VDR-Taq1T/C polymorphisms. In addition, no association of the CCR5D32 SNP with the disease was found (14). These findings underscore the significant influence of immunogenetic factors on the outcome of chronic HBV infection Moreover, cytokine receptors like TNF-α, IL-2R, IL-16, IL-10 and IL-10R are significantly increased in HBV-infected patients (7, 31-33) .

On the other hand, the effect of IL10 -1082A>G and TNFA -308G>A on susceptibility to HCV infection was investigated in the Brazilian population. Patients with the IL10 -1082A>G polymorphism had a higher HCV viral load. The patients with chronic HCV infection did not have TNFA –308G>A polymorphism, and its absence showed the protective role of TNF -308G>A in HCV infection (34). A study on Iranian subjects indicated a possible association between IL-10 promoter polymorphism (-1082A>G) and HCV infection (20). On the other hand, in another study on the Iraqi population, the effect of IL6 and IL4RA polymorphisms on HBV and HCV infection was investigated, and rs1800795 was significantly associated with HBV but not with HCV infection. IL6 rs1800797 had an association with both HBV and HCV infections. IL4RA rs1801275 had no association with HBV or HCV infection (35). Moreover, HBV-infected patients in India were investigated for the association of IL18 at position -607 with HBV infection. People with allele A at position -607 were protected against HBV infection. However, for position 137, no significant difference was observed between controls and cases (36).

In some of the included studies there was no enough clinical information which may affect the quality check of the studies. There are also some gaps in the information about sample size and case/control matching method. Some studies were also underpowered. These studies' limitations affected the range of quality control because of such limited evidence.

Conclusion

The polymorphisms of genes involved in the secretion of immune factors, cytokines, interleukins, and their receptors are associated with the risk of HBV and HCV infections in the Iranian population. Moreover, the extracellular and intracellular signaling pathways and the regulating molecules of these processes can be considered important factors in the spread of these viral infections. In the future, to pave the road to the personalized medicine, studies with a larger sample size should be conducted to validate the association of polymorphisms in these genes where these results can identify populations with a higher risk of infection and help take preventive measures to reduce the spread of the disease.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

No financial support was received for this study.

Conflict of interest

The authors declared no conflict of interest in this work.

References

1. Razavi-Shearer D, Gamkrelidze I, Nguyen MH, et al (2018). Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol,* 3 (6):383-403.
2. Clements CJ, Coghlan B, Creati M, Locarnini S, Tedder RS, Torresi J (2010). Global control of hepatitis B virus: does treatment-induced antigenic change affect immunization? *Bull World Health Organ,* 88 (1):66-73.
3. Zhao J, Zhang X, Fang L, Pan H, Shi J (2020). Association between IL28B polymorphisms and outcomes of hepatitis B virus infection: a meta-analysis. *BMC Med Genet,* 21:88.
4. Wei Y, Zhao Z, Wang Z, Zhang K, Tang Z, Tao C (2021). Relationships between IL-1β, TNF-α genetic polymorphisms and HBV infection: A meta-analytical study. *Gene,* 791:145617.
5. Aleagha O, Oltulu P, Sadeghi M (2020). Association between interleukin 6 polymorphisms (rs1800796, rs1800795, rs2069837, rs17147230, and rs1800797) and hepatocellular carcinoma susceptibility: a meta-analysis. *Clin Exp Hepatol,* 6 (4):359-366.
6. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al (2021). PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev,* 10:39.
7. Ahmadabadi BN, Hassanshahi G, Arababadi MK, Leanza C, Kennedy D (2012). The IL-10 promoter polymorphism at position -592 is correlated with susceptibility to occult HBV infection. *Inflammation,* 35 (3):818-21.
8. Attar M, Azar SS (2016). Interleukin-6-174 promoter polymorphism and susceptibility to hepatitis B virus infection as a risk factor for hepatocellular carcinoma in Iran. *Asian Pac J Cancer Prev,* 17 (5):2395-2399.
9. Azar SS, Mansoori M, Attar M, Shahbazi M (2016). Tumor necrosis factor alpha 308 G/A single nucleotide polymorphism and susceptibility to hepatocellular carcinoma via hepatitis B infection. *Asian Pac J Cancer Prev,* 17 (7):3381-3384.
10. Heidari Z, Moudi B, Sagheb HM, Moudi M (2016). Association of TNF-α gene polymorphisms with production of protein and susceptibility to chronic hepatitis B infection in the south east Iranian population. *Hepat Mon,* 16 (11): e41984.
11. Abdolmohammadi R, Azar SS, Khosravi A, Shahbazi M (2016). CCR5 polymorphism as a protective factor for hepatocellular carcinoma in hepatitis B virus-infected Iranian patients. *Asian Pac J Cancer Prev,* 17 (10):4643-4646.
12. Fatemipour M, Arabzadeh SAM, Molaei H, et al (2017). Evaluation of STAT3 rs1053004 single nucleotide polymorphism in patients with chronic hepatitis B and hepatocellular

carcinoma. *Cell Mol Biol (Noisy-le-grand),* 63 (12):45-50.
13. Moudi B, Heidari Z, Mahmoudzadeh-Sagheb H (2020). Polymorphisms of BIRC5 Gene is Associated with Chronic HBV Infection in Iranian Population. *Indian J Clin Biochem,* 35:158-168.
14. Moudi B, Heidari Z, Mahmoudzadeh-Sagheb H (2019). CCR5, MCP-1 and VDR gene polymorphisms are associated with the susceptibility to HBV infection. *Indian J Clin Biochem,* 34:407-417.
15. Khanizadeh S, Hasanvand B, Nikoo HR, et al (2019). Association between miRNA-146a rs2910164 (G/C) polymorphism with the susceptibility to chronic HBV infection and spontaneous viral clearance in an Iranian population. *J Med Virol,* 91 (6):1063-1068.
16. Ghasemian N, Shahbazi M (2016). Interferon gamma gene polymorphism (+ 874 T> A) and chronic hepatitis B in the population of Gorgan, North-Eastern Iran. *Jundishapur J Microbiol,* 9 (8): e33639.
17. Koolivand M, Allamehzadeh Z, Ahmadi A, et al (2020). The study of IFNL3 gene Rs12979860 polymorphism in the hepatitis C virus patients and healthy population in Tehran Province, Iran. *Jundishapur J Microbiol,* 13 (5): e95798.
18. Nasab SDM, Baharlou R, Piroozmand A, et al (2015). Distribution of IL-28B genotypes in patients with hepatitis C and healthy individuals in Jahrom city. *Gastroenterol Hepatol Bed Bench,* 8 (4):278-87.
19. Moudi B, Heidari Z, Mahmoudzadeh-Sagheb H, et al (2016). Association between IL-10 gene promoter polymorphisms (-592 A/C,-819 T/C,-1082 A/G) and susceptibility to HBV infection in an Iranian population. *Hepat Mon,* 16 (2): e32427.
20. Sepahi S, Pasdar A, Ahadi M, Gerayli S, Rostami S, Meshkat Z (2014). Haplotype analysis of interleukin-10 gene promoter polymorphisms in chronic hepatitis C infection: a case control study. *Viral Immunol,* 27 (8):398-403.
21. Mogensen TH (2022). Genetic susceptibility to viral disease in humans. *Clin Microbiol Infect,* 28 (11):1411-1416.
22. WHO (2021) Interim guidance for country validation of viral hepatitis elimination. Geneva, Switzerland: World Health Organization, 2021.
23. Forbester JL, Humphreys IR (2021). Genetic influences on viral-induced cytokine responses in the lung. *Mucosal Immunol,* 14 (1):14-25.
24. Guo X, Jin M, Yang M, Liu K, Li J-w (2013). Type 2 diabetes mellitus and the risk of hepatitis C virus infection: a systematic review. *Sci Rep,* 3:2981.
25. Jiang L, Kerchberger VE, Shaffer C, et al (2022). Genome-wide association analyses of common infections in a large practice-based biobank. *BMC Genomics,* 23 (1):672.
26. Huang S-C, Cheng P-N, Liu C-H, et al (2022). Serum cytokine/chemokine profiles predict hepatitis B reactivation in HBV/HCV co-infected subjects receiving direct-acting antiviral agents. *J Formos Med Assoc,* 121 (5):920-929.
27. de Brito WB, Queiroz MAF, Amoras EdSG, et al (2020). The TGFB1-509C/T polymorphism and elevated TGF-β1 levels are associated with chronic hepatitis C and cirrhosis. *Immunobiology,* 225 (5):152002.
28. Eskandari E, Metanat M, Pahlevani E, Nakhzari-Khodakheir T (2017). Association between TGFβ1 polymorphisms and chronic hepatitis B infection in an Iranian population. *Rev Soc Bras Med Trop,* 50(3):301-308.
29. Pereira FA, da Silva NNP, Rodart IF, Carmo TMA, Lemaire DC, Reis MG (2008). Association of TGF-β1 codon 25 (G915C) polymorphism with hepatitis C virus infection. *J Med Virol,* 80 (1):58-64.
30. Suneetha PV, Sarin SK, Goyal A, Kumar GT, Shukla DK, Hissar S (2006). Association between vitamin D receptor, CCR5, TNF-α and TNF-β gene polymorphisms and HBV infection and severity of liver disease. *J Hepatol,* 44 (5):856-863.
31. Tunçbilek S (2014). Relationship between cytokine gene polymorphisms and chronic hepatitis B virus infection. *World J Gastroenterol,* 20 (20):6226-35.
32. Das A, Ellis G, Pallant C, et al (2012). IL-10–producing regulatory B cells in the pathogenesis of chronic hepatitis B virus infection. *J Immunol,* 189 (8):3925-3935.
33. Behelgardi A, Hosseini SM, Mohebbi SR, et al (2015). A study on genetic association of

interleukin-16 single nucleotide polymorphism (rs1131445) with chronic hepatitis B virus infection in Iranian patients. *Jundishapur J Microbiol,* 8 (11): e23411.
34. Santiago AM, da Silva Graça Amoras E, Queiroz MAF, et al (2021). TNFA-308G> A and IL10-1082A> G polymorphisms seem to be predictive biomarkers of chronic HCV infection. *BMC Infect Dis,* 21(1):1133.
35. Al-Saffar OB, Ad'hiah AH (2020). Genetic variants in IL4RA, IL6, and IL12B genes and susceptibility to hepatitis B and C virus infections among Iraqi patients. *J Med Virol,* 92 (12):3448-3458.
36. Karra VK, Gumma PK, Chowdhury SJ, et al (2015). IL-18 polymorphisms in hepatitis B virus related liver disease. *Cytokine,* 73 (2):277-282.
37. Alizadeh AHM, Ranjbar M, Hajilooi M, Fallahian F (2006). Association of promoter polymorphism of the CD14 C (-159) T endotoxin receptor gene with chronic hepatitis B. *World J Gastroenterol,* 12 (35):5717-20.
38. Alizadeh AHM, Hajilooi M, Ranjbar M, Fallahian F, Mousavi SM (2006). Cytotoxic T-lymphocyte antigen 4 gene polymorphisms and susceptibility to chronic hepatitis B. *World J Gastroenterol,* 12 (4):630-5.
39. Sepahi S, Pasdar A, Gerayli S, Rostami S, Gholoobi A, Meshkat Z (2017). CTLA-4 gene haplotypes and the risk of chronic hepatitis C infection; a case control study. *Rep Biochem Mol Biol,* 6 (1):51-58.
40. Khanizadeh S, Ravanshad M, Mohebi S, Zali M, Talei G (2012). Association of polymorphism within promoter of the interferon-gamma receptor gene and HBV chronicity among Iranian patients. *International Journal of Infectious Diseases,* 16:e89.
41. Mirfakhar FS, Mohebbi SR, Hosseini SM, et al (2018). Evaluation of Interleukin-10 Gene Promoter Polymorphism (-819 C/T) in Patients with Chronic Hepatitis B Virus Infection. *J Isfahan Med Sch,* 35 (461):1852-1858.
42. Romani S, Hosseini SM, Mohebbi SR, et al (2014). Interleukin-16 gene polymorphisms are considerable host genetic factors for patients' susceptibility to chronic hepatitis B infection. *Hepat Res Treat,* 2014: 790753.
43. Larijani MS, Sadat SM, Nikbin M, et al (2016). Correlation study between IL-28B gene polymorphism (rs8099917SNP) and sustained virological response in Iranian patients with chronic hepatitis C. *Clin Lab,* 62 (3):417-423.
44. Larijani MS, Bahiraei N, Nikbin M, et al (2016). Lack of TNF-α gene polymorphism (rs1799724) association with sustained virological response in Iranian patients with chronic HCV infection. *Asian Pac J Cancer Prev,* 17 (8):3923-3927.
45. Ghavami SB, Mohebbi SR, Karimi K, et al (2018). Variants in two gene members of the TNF ligand superfamily and hepatitis C virus chronic disease. *Gastroenterol Hepatol Bed Bench,* 11 (Suppl 1):S66-S72.
46. Moudi B, Heidari Z, Mahmoudzadeh-Sagheb H, Hashemi M (2016). Gene polymorphisms of macrophage migration inhibitory factor affect susceptibility to chronic hepatitis B virus infection in an Iranian cohort. *Microbiol Immunol,* 60 (6):390-396.
47. Eskandari E, Dahmardeh T, Safdari V, Khosravi S, Pahlevani E (2017). HLA-G gene 14-bp deletion variant protects Iranian subjects against chronic hepatitis B infection. *Int J Immunogenet,* 44 (6):322-327.
48. Fattahi S, Karimi Alivije M, Babamahmoodi F, et al (2018). Cytochrome P450 genes (CYP2E1 and CYP1A1) variants and susceptibility to chronic hepatitis B virus infection. *Indian J Clin Biochem,* 33:467-472.
49. Moudi B, Heidari Z, Mahmoudzadeh-Sagheb H, Farrokh P (2018). The relationship between L-leucine-7-amido-4-methyl coumarin 1 gene polymorphism and susceptibility to the chronic hepatitis B virus infection in an Iranian population. *Res Med Sci,* 23:62.
50. Ayatollahi J, Heidari FS, Sharifyazdi M, et al (2019). Polymorphism of IL-12 gene (rs568408G/A) and susceptibility to chronic hepatitis B virus infection in the central area of Iran. *Rev Med Microbiol,* 30 (2):122-127.
51. Zangi M, Bakhshandeh A, Mehrpouya M, Shahbazi M (2019). Association of Interleukin 13/+ 110 Gene Polymorphism with Hepatitis B Virus Infection in Golestan Province, Northern Iran. *Jundishapur J Microbiol,* 12 (3): e68270.

52. Heidari Z, Moudi B, Mahmoudzadeh-Sagheb H (2020). Interferon gamma gene polymorphisms and chronic hepatitis B infections in Iranian population. *Turk J Gastroenterol,* 31 (7):515-517.
53. Bahrami A, Parsania M, Pourfathollah AA, Haghighat S, Sharifi Z (2020). Association of VDR (rs2228570, rs731236, rs7975232, rs1544410) and DBP (rs7041) genes polymorphisms with chronicity of hepatitis B in Iranian patients. *Gene Rep,* 19:100615.
54. Sarrafnia H, Mohebbi S, Ashrafi F, et al (2020). Genetic variation of Interleukin 18 gene (rs360719) and susceptibility to chronic hepatitis B virus infection. *Int J Infect Dis,* 101:523.
55. Tayefinasrabadi H, Mohebbi SR, Hosseini SM, et al (2020). Association of Interleukin-17 gene polymorphisms with susceptibility to chronic hepatitis B virus infection and clearance in Iranian population. *Microb Pathog,* 144:104195.