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Review

Gene polymorphisms of interferons and their receptors in chronic hepatitis B virus infection and hepatocellular carcinoma

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ABSTRACT

Chronic hepatitis B (CHB) is a serious disease caused by the hepatitis B virus (HBV). CHB can lead to liver cirrhosis and hepatocellular carcinoma (HCC). Strong evidence for the effect of host genetics has been previously reported. Hence, the difference in host genetics might affect the various outcomes of HBV infection. Polymorphisms in genes encoding interferons (IFNs) and interferon receptors such as IFN-α, IFN-γ, IFN-λ, IFNAR1, IFNAR2, IL10R2/IL10RB, IFNGR1, and IFNGR2 have been reported to be responsible for susceptibility to CHB infection. In this review, the current information in the literature on the association between gene polymorphisms of IFNs and their receptors and chronic HBV infection is summarized. This information can be used to determine the risk for CHB infection and/or the development of liver cancer. In addition, the knowledge about genetic polymorphisms could be applied for prevention, treatment of HBV infections, and the development of new therapeutics for HBV patients.

KEYWORDS: hepatitis B virus, hepatocellular carcinoma, polymorphism, interferon, IFN receptor.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health problem. Approximately 240 million people worldwide are chronically infected with HBV. This virus leads to liver cirrhosis and hepatocellular carcinoma (HCC) and causes 780,000 deaths per year. The prevalence of HBV infection is highest in sub-Saharan Africa and East Asia. High rates of chronic infections are found in the southern parts of Eastern and Central Europe, the Amazon, the Middle East, and the Indian subcontinent. However, chronic HBV infection is rare in the population of Western Europe and North America countries [1]. Following primary infection, some people rapidly develop liver disease, while others become silent carriers. A number of risk factors implicated in HBV-induced liver disease have been reported, such as alcohol, age, sex, HBV genotypes and genetic factors [2]. A study in Chinese twins provides a strong evidence for a genetic effect, which showed a higher concordance rate for the persistence of hepatitis B e-antigen (HBeAg) in monozygotic twins as compared with dizygotic twins [3].

Single nucleotide polymorphism (SNP) is a DNA sequence variation occurring commonly among people. It is the replacement of a nucleotide with another nucleotide. SNPs in promoter region may alter transcription factor binding site leading to different mRNA levels. Non-synonymous SNP in

exon may affect the amino acid sequence of predicted proteins. This change may affect the protein functions by altering the catalytic activity or the receptor-ligand contact. SNPs in intron are most commonly found at the beginning and the end of the donor and acceptor consensus splice sequence. This may cause either exon skipping or utilization of cryptic splice sites, resulting in the absence of normally spliced mRNA [4]. In addition, SNPs in the three prime untranslated region (3'-UTR) may affect translational level by changing miRNA-binding targets [5]. Individuals with these polymorphisms may be at a risk for developing HBV-related liver disease or have a protective effect against it.

Interferons (IFNs) are potent immune-modulatory cytokines that were discovered in 1957 by Isaacs and Lindenmann [6]. IFNs have been classified into three major types based on their structure and type of specific receptors; type I (IFN-I), II (IFN-II), and III (IFN-III) as showed in Table 1. IFN-I consists of IFN-α subtypes (13 subtypes), IFN-β, IFN-ε, IFN-κ, and IFN-ω. The activity of all IFN-I members is mediated by a unique heterodimeric receptor, interferon-α/β receptor (IFNAR), which is composed of IFNAR1 and IFNAR2 [7]. However, the main subtypes of IFN-I are IFN-α and IFN-β which are involved in immune response against viral infection. Another type of IFN is IFN-γ (IFN-II) that binds to IFN-γ receptor with two different subunits, IFNGR1 and IFNGR2 [8]. IFN-γ plays a role in innate and adaptive immunity against intracellular pathogens, especially viruses. It is an important activator of macrophages and an inducer of maturation and differentiation of various cell types. Moreover, this IFN-II is involved in immune response of type 1 helper T cell (Th1) [9]. For the IFN-III group, three distinct proteins, IFN-λ1, IFN-λ2, and IFN-λ3 (also called IL-29, IL-28A, and IL-28B, respectively) were recently identified. The members of this IFN group were found to interact with the unique receptors composed of the IFNLR1 chain (also known as IL-28 receptor alpha; IL-28AR) and the interleukin-10 receptor 2 subunit (IL-10R2). Although IFN-III structure is similar to IFN-II (IFN-γ), but the function is identical with IFN-I (IFN-α/β) in terms of protection from viral infection [10]. To stimulate the antiviral response, all IFNs can trigger the janus kinase (JAK) and signal transduction and activators of transcription (STAT) signaling pathways *via* their receptors to induce the expression of numerous IFN-inducible genes [11].

The information on IFN and IFN receptor gene polymorphisms extracted from the dbSNP and Ensembl databases (accessed 03 June 2018) [12, 13] is illustrated in Figure 1. There are 241,975 SNPs on IFN and IFN receptor genes in total. However, only 5,741 SNPs are considered as common variants with a global minor allele frequency (MAF) value ≥ 0.05. All of these variants were supported by reliable sources/evidences, for example, they

Table 1. Classification of IFNs and their biological information.

IFN type	Class	Sources	Gene location	# of genes	IFN gene symbols	Receptor gene symbols
I	IFN-α	Leukocytes	Chr. 9	13	*IFNA1* to *13*	*IFNAR1* *IFNAR2*
	IFN-β	Fibroblasts		1	*IFNB1*	
	IFN-ε	Epithelial cells of reproductive organs		1	*IFNE*	
	IFN-κ	Undefined		1	*IFNK*	
	IFN-ω	Leukocytes		1	*IFNW1*	
II	IFN-γ	T cells, NK cells	Chr. 12	1	*IFNG*	*IFNGR1* *IFNGR2*
III	IFN-λ1(IL-29) IFN-λ2(IL-28A) IFN-λ3 (IL-28B)	Dendritic cells and macrophages	Chr. 19	3	*IFNL1* to *3*	*IFNLR1* *IL10RB*

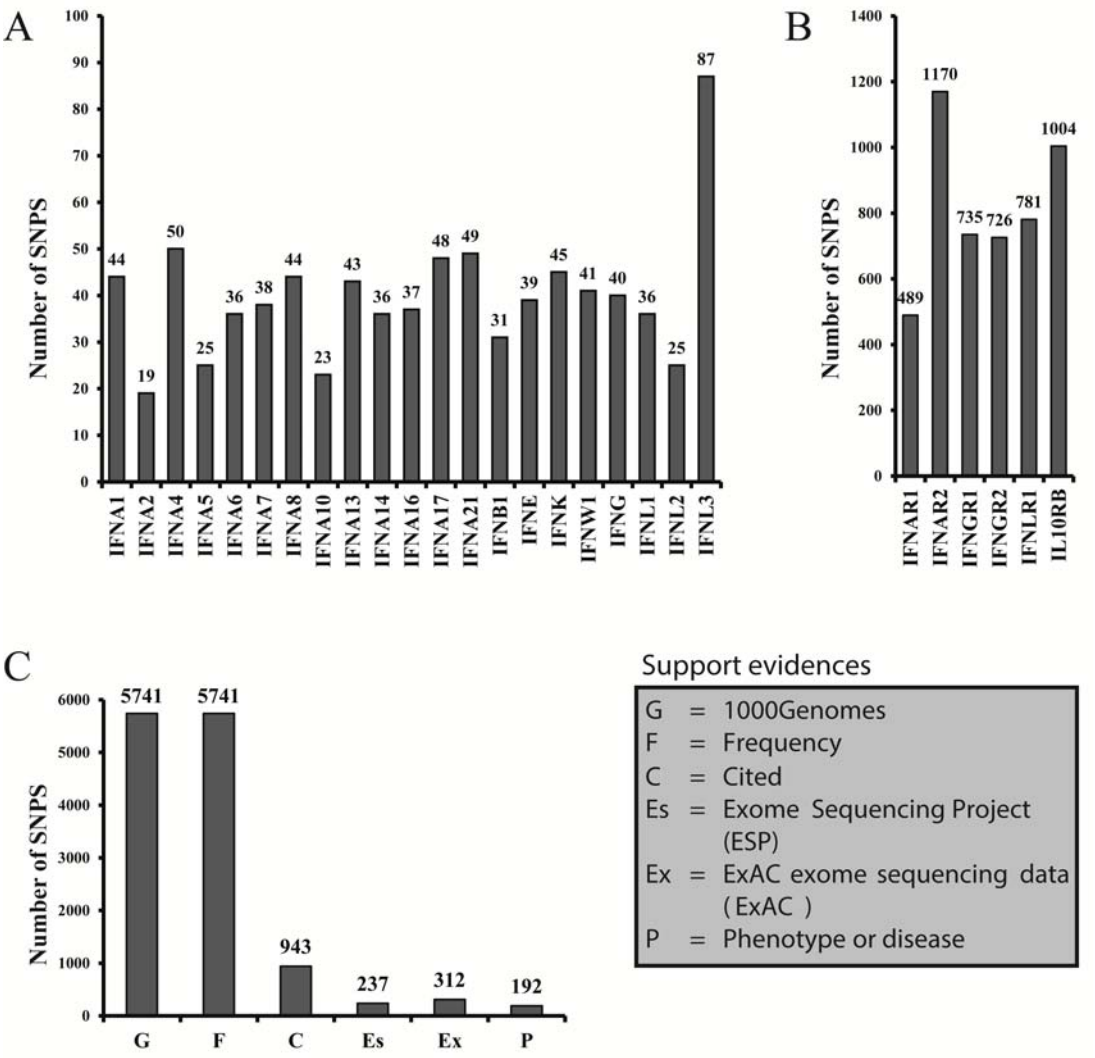

Figure 1. SNP data of IFN and IFN receptor genes extracted from dbSNP [12] and Ensembl [13] databases. The upper bar charts indicate the numbers of SNPs with a global minor allele frequency score (MAF) ≥ 0.05 of IFN (**A**) and IFN receptor genes (**B**). All 5,741 SNPs with global MAF ≥ 0.05 were further investigated for evidences that supported these variants and plotted as a bar chart (**C**).

were discovered by the 1,000 genomes project, Exome Sequencing Project (ESP), or ExAC exome sequencing data. These SNPs can be a potential factor that causes diseases in human.

In this review, we focus on the effect of IFN and IFN receptor gene polymorphisms on the susceptibility to CHB infection and HBV-related HCC as summarized below (Table 2).

IFN-α

IFN-α is a cytokine involved in innate immunity to protect viral infection. This cytokine has been shown to inhibit HBV replication in the liver of HBV-transgenic mice and widely used in the treatment of chronic HBV infection [14, 15]. The IFN-α family is comprised of IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17, and IFNA21 [16]. Only IFNA1 and IFN5 have been investigated in the association between SNP within the promoter region and susceptibility to chronic HBV infection and the development of HCC in Thai population. Our study in 2013 showed that A allele of -1823G/A SNP(rs1332190) within IFNA1 gene was significantly associated with an increased risk

Table 2. Effect of IFN and IFN receptor gene polymorphisms on the susceptibility to chronic HBV infection and HCC.

Gene	SNP	Population	Effect	Reference
IFN-α	IFNA1 (rs1332190/ -1823G/A)	Thai	chronic HBV infection	[17]
	IFNA1 (rs1332190/ -1823G/A) - IFNA5 (rs3758236/ -2529A/T)	Thai	chronic HBV infection	[17]
	IFNA1 (rs202055606/-2C/T)	Brazilian	protective effect to chronic HBV infection	[18]
IFN-γ	rs2430561 / +874T/A	Chinese, Korean, Turkish, India, Syrian	chronic HBV infection and/or HBV-related HCC	[20-26]
	rs2430561 / +874T/A	Japanese, Korean, Chinese, Iranian	no effect	[30-33]
	CA12 repeat microsatellite / rs3138557 - rs2430561 / +874T/A	Korean	HBV-related HCC	[23]
	Haplotype AG of rs2430561 / +874T/A and rs1861494 / +2109A/G	Chinese	HBV infection	[20]
	Haplotype AA of rs2430561 / +874T/A and rs1861494 / +2109A/G	Chinese	HBV-related liver cirrhosis	[32]
	rs181407537/-5A/G	Brazilian	no effect	[18]
IFN-λ	IFN-λ3/IL28B rs12979860 and/or rs12980275 and rs8099917	Chinese, Thai	chronic HBV infection and/or HBV-related HCC	[35-37]
	Haplotype CG of IFN-λ3/IL28B rs12979860 and rs8099917	Chinese	seroclearance of hepatitis B surface antigen	[38]
	IFN-λ3/IL28B rs12979860 and/or rs12980275 and/or rs8099917	Caucasian, Chinese, Korean, Iranian	no effect	[39-42]
IFNAR	IFNAR1 rs1012335, rs2843710, rs2257167, and rs17875871	Chinese, Vietnamese, Caucasian, Thai	chronic HBV infection and/or HBV-related HCC	[5, 45-51]
	IFNAR1 rs1012335, rs2843710, rs2257167, and rs17875871	Gambian	no effect	[44]
	IFNAR1 (rs2850015/-97T/C)	Brazilian	low HBV-DNA level	[18]
	IFNAR2 rs2229207 (F/S)	Gambian, Thai	chronic HBV infection	[44, 53]
	IFNAR2 rs2229207 (F/S)	Chinese	high HBV-DNA level	[52]
	IFNAR2 rs2229207 (F/S)	Chinese	no effect	[54]
IL-10R2/ IL-10RB	IL-10RB rs2834167 (K/E)	Gambian, Chinese,	persistence of HBV infection	[44, 54, 55]
	IL-10RB rs2834167 (K/E)	Chinese, Thai	protective effect to HBV infection	[52, 53]

Table 2 continued..

IFNGR	IFNGR1 [rs2234711 (-56C/T), rs1327474 (-611A/G), rs7749390 (+95C/T) and rs3799488 (+20685A/G)]	Chinese, Turkish	chronic HBV infection	[27, 56, 57]
	IFNGR2 [rs1059293 (+33,844A/G)]	Chinese	chronic HBV infection	[56]
	IFNGR1 [rs2234711 (-56C/T) and rs7749390 (+95C/T)] and IFNGR2 [rs9808753 (+11,463)]	Korean	no effect	[30]
	IFNGR1 [rs1327474 (-611A/G), rs11575936 (+40G/A), rs11754268 (+130A/G), rs3799488 (+20685A/G) and rs1887415 (+21227T/C)]	Chinese	no effect	[56]

for chronic HBV infection as compared to healthy individuals and self-limited HBV group. In addition, the interaction between IFNA5 (-2529A/T, rs3758236) and IFNA1 (-1823G/A, rs1332190) genes that conferred the risk to chronic HBV infection was found in our study [17]. However, functional significance of these two polymorphisms has not yet been determined. Furthermore, CT genotype and T allele of IFNA1 (rs202055606) in chronic HBV Brazilian patients were associated with HBV clearance when compared to immune controls [18].

IFN-γ

IFN-γ is a pleiotropic cytokine that regulates the activity of both innate and adaptive immune responses. A SNP located in the IFN-γ gene intron (+874T/A, rs2430561) has been widely studied. Previous study has shown that this position is a specific binding site for the NF-κB transcription factor, affecting expression of IFN-γ gene. The T allele of +874T/A polymorphism correlated with high IFN production when compared to the A allele [19]. Many publications have shown that the IFN-γ + 874AA genotype and/or +874A allele is involved in chronic HBV infection and/or HBV-related HCC [20-26]. In addition, several recent meta-analyses confirmed these findings [27-29]. However, some studies observed no statistically significant association of this SNP with susceptibility to persistent HBV infection [30-33]. The combination between other polymorphisms and IFN-γ + 874T/A has been analyzed. A study revealed that a CA_{12} repeat microsatellite (rs3138557) combined with IFN-γ + 874T/A is associated with susceptibility to HBV-related HCC [23]. The CA_{12} repeats were also shown to be associated with high IFN-γ production in stimulated lymphocytes *in vitro* [34]. Moreover, haplotype AG of +874T/A and +2109A/G (rs1861494) of IFN-γ increased the risk for HBV infection in the Chinese population [20]. Nevertheless, a recent study showed that haplotype AA of +874T/A and +2109A/G increased the development of HBV-related liver cirrhosis [32]. Additionally, another SNP (rs181407537) of IFN-γ studied in Brazilian patients showed no significant association with chronic HBV infection [18].

IFN-λ

IFN-λ is comprised of three molecules; IFN-λ1 (IL29), IFN-λ2 (IL28A), and IFN-λ3 (IL28B). These molecules belong to type III interferon family that plays a role in immune defense against viral infection [10]. Several studies have shown that genetic polymorphisms of the IFN-λ3 or IL28B gene (rs12979860 and/or rs12980275 and rs8099917) were significantly associated with susceptibility to chronic HBV infection and/or development of HCC [35-37]. Moreover, a study reported that IL28B polymorphisms influence seroclearance of hepatitis B surface antigen in chronic HBV infection [38]. In contrast, some studies showed negative associations between IL28B polymorphisms and outcomes of HBV infection [39-42]. A most recent meta-analysis showed that T allele of IL28B rs12979680 increased the risk of HBV infection in Chinese population, but not Asian population. For IL28B rs8099917, no association between this SNP and HBV infection in Chinese and Asian populations was found [43].

IFNAR

IFNAR is a receptor binding to type I IFNs. This receptor consists of two subunits IFNAR1 and IFNAR2. Both of them belong to a cluster of class II cytokine receptor genes that was identified as a major susceptibility locus [44]. Association between SNPs (rs1012335, rs2843710, rs2257167, and rs17875871) of the IFNAR1 gene and chronic HBV infection and/or the development of HCC in Chinese, Vietnamese, Caucasian, and Thai populations has been reported [5, 45-51]. However, Frodsham A. J. *et al*. (2006) reported that there was no significant association between these SNPs of IFNAR1 and chronic HBV infection in the Gambian population. In addition, this study also showed that nonsynonymous SNP (rs2229207, F/S) of IFNAR2 gene affected the outcome of persistent HBV infection [44]. Besides, several studies in Asian populations reported that this functional SNP was associated with the risk for high viral loads [52] and chronic HBV susceptibility [53]. However, these findings were contradicted with the findings published by Chen *et al*. [54]. Another SNP of IFNAR1 (rs2850015) has been studied in Brazilian population [18]; Santos *et al*. found no significant association with chronic

HBV infection. However, this SNP correlated with the low level of HBV-DNA [18].

IL-10R2

IL-10R2 (also called IL-10RB) is a receptor of type III IFN that complex with IFNLR1. The common K allele of the SNP IL-10RB-K47E (rs2834167, A/G) was associated with persistence of HBV infection [44, 54, 55]. This K allele has been associated with lower receptor expression, which leads to the decrease of signal transduction [44]. Nevertheless, these results differed from the studies of Gong Q. M. *et al.* and Romporn S. *et al.* who found the protective effect of this polymorphism [52, 53].

IFNGR

IFNGR is a receptor of IFN-γ which is made up of IFNGR1 and IFNGR2 subunits. The relation of IFNGR1 and IFNGR2 polymorphisms with HBV persistence has been studied. Several SNPs in IFNGR1 [rs2234711 (-56C/T), rs1327474 (-611A/G), rs7749390 (+95C/T) and rs3799488 (+20685A/G)] and a SNP in IFNGR2 [rs1059293 (+33,844A/G)] have been associated with chronic hepatitis B infection [27, 56, 57]. However, a study found no relationship between SNP markers in the IFNGR1 [rs2234711 (-56C/T) and rs7749390 (+95C/T)] and IFNGR2 [rs9808753 (+11,463)] genes and susceptibility to persistent HBV infection [30]. In addition, association between several SNPs in the IFNGR1 [rs1327474 (-611A/G), rs11575936 (+40G/A), rs11754268 (+130A/G), rs3799488 (+20685A/G) and rs1887415 (+21227T/C)] and susceptibility to chronic HBV infection was not found in Zhou *et al.*'s study [57].

CONCLUSION

In this review, we summarized a number studies showing association between gene polymorphisms of interferons and their receptors and chronic HBV infection and/or disease progression. However, the results from different ethnic groups remain controversial. In statistics, meta-analysis is a powerful tool to summarize these inconsistent findings from different studies. Hence, meta-analysis would be needed in the future to provide more convincing conclusions. In addition, further summarization of IFN and IFN receptor gene polymorphisms involving clinical course of the infection, the response to treatment and vaccination is needed. These information will be beneficial in that they can be applied for the prevention and treatment of HBV infection and for the development of new therapeutic approaches in the future.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest to disclose.

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