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Research Article

Relationship between Il28b Gene Polymorphisms and the Risk of Hepatocellular Carcinoma Development within Vietnamese Hepatitis B Virus Carriers

Abstract

IL28B's SNPs are considered the most important host factors predicting the success of Peg-INF alpha/ribavirin based regimens against Hepatitis C virus (HCV) infection. However, the associations of HBV mediated etiologies have not been well documented. This study investigated the relationship between the three most clinically relevant IL28B SNPs (rs8099917, rs12980275, and rs12979860) with the risk of HBV/HCV infection and HCC development within Vietnamese HBV carriers. By using kinetics and allele specific real-time PCR, the study demonstrated holders of the T/G allele at SNP rs8099917 were less susceptible to HBV/HCV infection. Notably, HBV carriers with the SNP rs8099917 T/G allele were at lower risk of being transformed into HCC. However, because of a small sample size, statistical analysis did not reach significance to demonstrate an association between frequencies of IL28B SNPs and HBV mediated HCC development, even though only the minor allele carriers (either 4 G/G cases of rs8099917 or one T/T case of rs12979860) were recorded in the HCC group.

Introduction

Approximately 170 million people worldwide are chronically colonized with hepatitis C virus (HCV) and only 20-30% of that population spontaneously recover, while the remaining population progress to liver cirrhosis [1] or hepatocellular carcinoma (HCC) [2]. Unfortunately, no effective HCV vaccine is available. Studies have shown the immune response and host factors (genetics) are the important determinators for the prediction of HCV infection [3]. Cytokines are assumed to play a critical role in the pathogenesis of HCV infection by influencing the innate and adaptive immune response and immune system activation. These are implicated in the diverse clinical outcomes of HCV infection, including the susceptibility, spontaneous clearance, and viral persistence [4,5]. The cytokine IL-28B is a member of the type III IFN family, also named IFN-λ, which includes IL-28A and IL-29 that form a cytokine encoding gene cluster on human chromosome 19. It was reported that genetic variants of IL-28B, including the three most clinical relevant *rs12979860*, *rs12980275*, and *rs8099917* not only play an important role in the natural clearance of hepatitis C virus (HCV) [6], but also exhibit strong prognostic value to the clinical outcome of anti-HCV therapy [7,8].

Another significant cause of liver disease is hepatitis B virus (HBV). Of the 2 billion infected throughout the world, more than 350 million are chronic viral carriers [9]. HBV infection causes a wide range of diseases that can lead to liver cirrhosis and hepatocellular carcinoma (HCC). These include asymptomatic chronic HBV carriers, acute hepatitis B, or active chronic hepatitis B; however, the reason for this variation is still controversial [10]. Although recent studies reported IL28B polymorphism is related to the clinical presentation to HBV infection, the connection between IL28B polymorphisms to the natural eradication of hepatitis B virus (HBV) or if it mediates HBV related etiologies remains unknown. While some studies reported non-association of IL28B genotypes to either hepatitis B virus clearance or hepatitis B antigen clearance or hepatocellular carcinoma occurrence [11,12], others provided evidence of a significant relationship between genetic variants of IL28B to both patients' history of HBV infection and the risk of acquiring HCC or other HBV mediated diseases [11,13].

While some of the eight million HBV carriers in Vietnam will spontaneously recover from acute virus infections, the rest will either develop liver cirrhosis or HCC. Many questions regarding the molecular interactions between host genetic

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factors that include IL28B gene polymorphisms, which may become HBV infection or may cause the transition from chronic HBV infection into liver cirrhosis or liver cancer, are still ambiguous. Therefore, in the current study, we analyze the relationship between genetic variants at SNP rs8099917, rs12980275, and rs12979860 to the relevance of HBV mediated liver diseases within ethnic Vietnamese.

Study Subjects and Methods

Study subjects

125 Vietnamese HBV infected and 99 HCV infected patients were enrolled at 108 Military Hospital (108 Institute of Clinical Medical and Pharmaceutical Sciences), Hanoi, Vietnam in 2010 and 2011. 81 healthy Vietnamese blood donors were used as a control group. Study participants did not have a history of alcohol or drug abuse and did not receive any antiviral or immunosuppressive therapy before or during the course of this study. The 125 symptomatic HBV-infected patients were categorized into three groups according to clinical, biochemical, and serological diagnoses as detailed elsewhere [14]: 32 patients with chronic active HBV, 28 patients with liver cirrhosis [1], and 65 HBV infectd hepatocellular carcinoma (HCC) patients. Biopsies were taken from all patients with suspected chronic HBV and then classified on the basis of detailed histological examination into those with or without evidence of either cirrhosis or carcinoma. In the latter case, the degree of differentiation was noted. All individuals included in the HCC group had late stage carcinoma. Individuals with neither cirrhosis nor carcinoma were attributed a histological activity index according to the scheme described by Luo et al. [15]. 99 chronic C hepatitis (CHCs) patients were treated by IFN plus Ribavirin regimen. All were single infected and were negative for HIV antibodies.

Liver biochemical tests

Albumin, globulin, total bilirubin, direct bilirubin, ALT, AST levels were measured in an auto-analyser (Hitachi model 736 automatic analyser; Hitachi, Tokyo, Japan).

Hepatitis B virus markers

HBsAg, anti-HBc-IgM, anti-HBcIgG, HBeAg and anti-HBe were measured using commercially available immunoassay kits (General biologicals Corp., Taiwan and DiaSorin, Saluggia, Italy).

Cancer markers

Alpha-feto protein (AFP) was measured by a commercial radioimmunoassay (General biologicals Corp., Taiwan).

IL-28B genotyping

IL-28B genotyping was identified by using Sybr green based allele specific real time PCR, which was first described by Søren Germer [16] and then was applied by Thomas R. O'Brien [17]. When investigating genetic variants at one SNP position, then two real-time PCR reactions are used with corresponding forward allele specific primers. The 3' prime end of forward allele specific primers are exactly complimentary to the inspected allelic variation nucleotides and the fluorescent signal intensity is correlated to an allelic variant abundance. Therefore, if the patient DNA is homozygous for the inspected SNP, then two differentiated fluorescent curves are recorded; the early amplification is the true specific signal and delayed amplification is the mismatched signal (figure 1 - lower left panel). If the patient's DNA sample is heterozygous, then each allele equally accounts for 50 percent of the DNA load and the corresponding fluorescent signal curves are almost undistinguishably overlapped ((ΔCt ≤1) [16,17] (Figure 1 - lower right panel). The Thomas R. O'Brien's primer sets were used in this study and two more allele specific forward primers were designed (from 5' to 3') 12980275fwA: AGAAGTCAAATTCCTAGAAACG; 12980275fwG: GAGAAGTCAAATTCCTAGAAACA. The two additional primer sets were paired with one common reverse primer 12980275ReG: GAATCTCTGTACCCATTAAACAACAACT to effectively discriminate the IL28B genetic variants of Vietnamese HCV carriers at positions rs8099917, rs12979860, and rs12980275.

Statistical analysis

The data was expressed as the median (range), n (%), or n as appropriate. Observed numbers of each genotype were compared with the expected values in order to test whether the sample was in Hardy-Weinberg equilibrium using the chi-Square test with one degree of freedom. The odds ratio (OR)

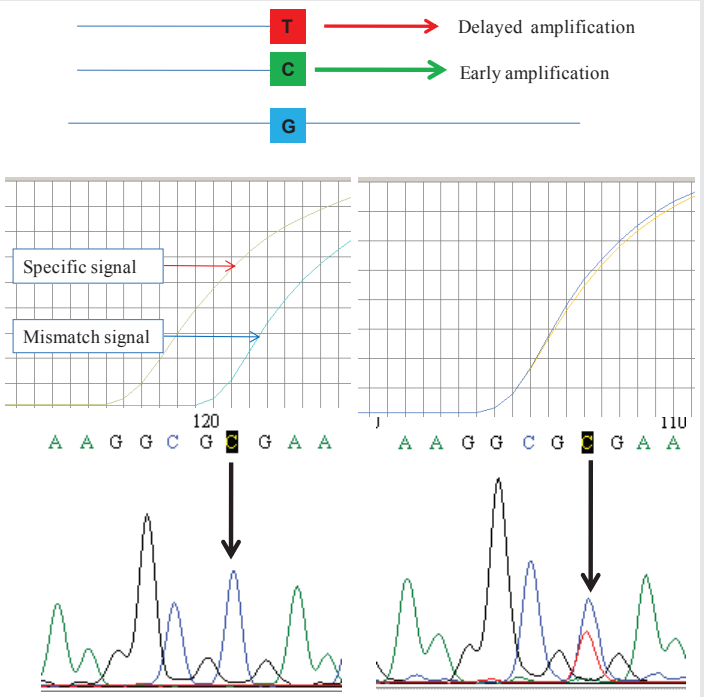

Figure 1: Methodology used for genotyping the IL28B gene: Two real-time PCR reactions were used with suitable forward allele specific primers. The 3' prime ends of forward allele specific primers were exactly complimentary to the inspected allelic nucleotides (upper panel). Therefore, the fluorescent signal intensity was correlated to allelic variant abundance. If the patient DNA was homozygous for the inspected SNP, then two differentiated fluorescent curves were recorded. The early amplification was the true specific signal whereas the delayed amplification was the mismatched signal (figure 1 - lower left panel). If the patient DNA sample was heterozygous, then each allele equally accounts for 50 percent of DNA load. Therefore, corresponding fluorescent signal curves are almost undistinguishably overlapped ((ΔCt ≤1) (16, 17) (figure 1 - lower right panel).

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was calculated to indicate the associated risk and presented with 95% confidence intervals (CI). A *P*-value <0.05 on a two-tailed test was considered statistically significant. Statistical analyses were performed with StatView (http://statview.com) and Stata 11 (http://stata.com/).

Ethical approval

All subjects were native Vietnamese and provided written informed consent for participation and for use of their genetic material for this study. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by the Institutional Review Board of the Tran Hung Dao Hospital, Hanoi, Vietnam.

Result

Holders of T/G heterozygous genotype at SNP rs8099917 are more protective against HCV infection

As seen in Table 1, neither the healthy cohort nor HCV carriers were infiltrated with homozygous minor alleles of the three concerned SNPs. However, frequency of homozygous major T/T genotype at rs8099917 in HCV carriers (95.96%) were significantly higher than that of the healthy group (83.95%) (p<0.01). Interestingly, those harboring the T/G heterozygous genotype of SNP rs8099917 were less susceptible to contract HCV than homozygous T/T genotype carriers at SNP rs8099917 [OR=0.22, 95% CI (0.05-0.75); χ^2=7.51, p<0.01]. As a result, the individual carrying a G allelic has a protective effect on HCV infection.

During initial analysis the co-distribution of rs12980275 and rs12979860 SNPs was observed: individuals who possess SNP at rs12980275 would also harbor SNP at rs12979860 and vice versa (data not shown). This redundancy deemed it unnecessary to record occurrences of all three concerned IL28 SNPs; therefore, the focus shifted to incidence of rs8099917 and rs12979860 for all subjects in the study.

Holders of single heterozygous genotypes at SNPs near IL-28B gene are more resistant against HBV infection

The purpose of this study was to examine the relationship between IL28B allelic genotype at the aforementioned SNPs and HBV infection by comparing allelic frequencies at two SNP positions (rs8099917 and rs12979860) between healthy and HBV infected groups (Table 2). Statistics revealed 6.4% of HBV infected groups and 16.05% of the healthy control cohort carried the heterozygous T/G genotype at rs8099917 [OR (95% CI) = 0.37 (0.13-1.02)]. Additionally, there was a significant reduction of the C/T heterozygous allele at SNP rs12979860 from 20.7% of the healthy group down to 10.4 % of the HBV infected group [OR (95% CI) 0.44 (0.18-1.04)]. From this it was concluded that heterozygous genotypes of each single SNP (rs8099917 and rs12979860) near IL28B protect the host against HBV infection.

Carriers of IL28B heterozygous T/G allele SNPs rs8099917 are lower risk of being transformed into hepatocellular carcinoma

In this study, it was statistically demonstrated that there is an association between genetic variants at two IL28B SNPs (rs8099917 or rs12979860) with either HBV or HCV susceptibility. Consequently, the relationship between genotypes of IL28B SNPs and the risk of developing liver cancer was investigated. As seen in Table 3, the occurrence of the IL28B heterozygous T/G allele at SNP rs8099917 among the HCC cohort is 4.61%, which is significantly (OR= 0.27 (0.05-1.06), p=0.038) less than that of the healthy group (16.05%). Higher frequencies of the rs12979860 T/G allele within the healthy group were observed in comparison to that of HBV infected HCC cohort; however, the sample size was not large enough to reach a significant statistical value (p= 0.057). Therefore, it can be concluded that carriers of heterozygous T/G allele at SNP rs8099917 are at lower risk of developing hepatocellular carcinoma.

Table 1: Allelic frequencies of rs8099917, rs12980275, rs12979860 in chronic C hepatitis and healthy cohort.

IL28 SNPs	allele	healthy cohort (n=81)	HCV (+) (n=99)	OR (95% CI)	χ2, p
rs8099917	T	0.9198	0.98	1	
	G	0.0802	0.02	0.94 (0.41-2.2)	0.02, >0.05
	T/T	68 (83.95)	95 (95.96)	1	
	T/G	13 (16.05)	4 (4.04)	0.22 (0.05-0.75)	7.51, <0.01
	G/G	0 (0)	0(0)	Not applicable	Not applicable
rs12979860	C	0.895 (145)	0.9293(184)	1	
	T	0.105(17)	0.0707(14)	0.65 (0.28-1.4)	1.33, >0.05
	C/C	64 (79.1)	85 (85.86)	1	
	C/T	17 (20.9)	14 (14.14)	0.62 (0.26-1.45)	1.46, >0.05
	T/T	0 (0)	0 (0.0)	Not applicable	Not applicable

Table 2: IL28B allelic frequencies distribution between healthy control and HBV carriers.

IL28 SNPs	allele	healthy cohort (n=81)	HBV (+) (n=125)	OR (95% CI)	χ2, p
rs8099917	T	0.9198 (149)	0.936 (234)	1	
	G	0.0802 (13)	0.064(16)	0.78 (0.34-1.82)	0.4, >0.05
	T/T	68 (83.95)	113 (90.4)	1	
	T/G	13 (16.05)	8 (6.4)	0.37 (0.13-1.02)	4.64, 0.03
	G/G	0 (0)	4 (3.2)	Not applicable	Not applicable
rs12979860	C	0.895 (145)	0.94 (235)	1	
	T	0.105 (17)	0.06 (15)	0.54 (0.24-1.2)	2.77, 0.09
	C/C	64 (79.1)	111 (88.8)	1	
	C/T	17 (20.9)	13 (10.4)	0.44 (0.18-1.04)	4.33, 0.037
	T/T	0 (0)	1 (0.8)	Not applicable	Not applicable

Table 3: Allelic frequencies and genotypes of SNPs near IL28B gene between healthy and HBV-induced HCC patients.

IL28 SNPs	Allele	healthy cohort (n=81)	HCC (n=65)	OR (95% CI)	χ^2, p
rs8099917	T	0.9198 (149)	0.915(119)	1	
	G	0.0802 (13)	0.085(11)	1.06 (0.41-2.66)	0.02, 0.89
	T/T	68 (83.95)	58 (89.23)	1	
	T/G	13 (16.05)	3 (4.61)	0.27 (0.05-1.06)	4.31, 0.038
	G/G	0 (0)	4 (6.16)	Not applicable	Not applicable
rs12979860	C	0.895 (145)	0.938(122)	1	
	T	0.105(17)	0.061(8)	0.56 (0.2-1.4)	1.74, 0.19
	C/C	64 (79.1)	58 (89.23)	1	
	C/T	17 (20.9)	6 (9.23)	0.39 (0.12-1.13)	3.61, 0.057
	T/T	0 (0)	1 (1.54)	Not applicable	Not applicable

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IL28B SNPs are not associated with the progression of HBV related diseases into hepatocellular carcinoma

Even though data revealed the heterozygous T/G allele at SNP rs8099917 is a host resistant factor linked to reducing the risk of liver cancer occurrence in HBV infected polulation, it is unknown if genetic variants of IL28B also associate to HBV mediated hepatocellular carcinoma development. The allelic frequencies at SNPs rs8099917 or rs12979860 between non-HCC patients carrying HBV (Non-HCC HBV) and HCC patients carrying HBV (HCC HBV) were compared. As seen in Table 4, the carriers of G allele or T/G genotype at SNP rs8099917 are higher in non-HCC patients carrying HBV compared to that of HCC patients carrying HBV. Due to the small sample size the study failed to reach a statistic significant level ($p>0.05$) and cannot conclude that genetic variants of IL28B were associated to HBV related chronic liver diseases developing into cancer.

Discussion

Human susceptibility to disease , including HCV or HBV infection, is not only dependent on genotypic features of the viral pathogens, but also host factors (traits of an individual person). The host factors play a crucial role in defining the natural responses to viral pathogen colonizations including HCV or HBV infection.

Recently, several studies have reported the value of single nucleotide polymorphisms (SNPs) near IL28B gene as the most important parameter to either predict the success of anti-HCV therapy or the vulnerability of some human populations to HCV infection [6-8,18]. It is not clear, however, whether IL28B genotypes also acquire some role in establishing the susceptibility of a given ethnicity to HBV infection or mediating the progression of HBV related diseases. There are some 8.4 million individuals living with chronic HBV infection in Vietnam and it was estimated that in 2005 this caused 23,300 HBV-related mortalities [19]. Information about factors including environment, alcohol abuse, and most notably the interaction between host factors and HBV or HCV infection are poorly reported. The lack of information between the recently characterized host genetic factors, IL28B genotypes with the susceptibility of HCV/HBV infection and risk of developing HCV/HBV related liver diseases, deemed it necessary to investigate.

Since the Sybr green based allele specific realtime PCR [16] is simplistic, it was possible to simultaneously screen study subjects for all three best characterized IL28B SNPs (rs8099917, rs12980275, and rs12979860). Until now, the distribution of IL28B SNPs among ethnic Vietnamese was investigated via the study of Dunford L. group using 368 HBsAg positive patient samples, which showed Vietnamese ethnicities had 86.41% of the C/C homozygous major allele, 13.04% of the C/T heterozygous, and 0.54% of the homozygous minor allele at SNP rs12979860 [20]. The allelic frequencies in the Dunford L. study were similar to what was exhibited in this study (Table 1). It can be concluded that the IL28B allelic distribution at rs12979860 in Vietnamese populations are robust. In this study, the statistical allelic frequency of rs8099917, rs12980275, and rs12979860 near the gene IL28B of the Vietnamese ethnicity was recorded: rs8099917 (83.95%), rs12979860 (79.1%), and rs12980275 (83.95%). When compared to Japanese ethnicity, the Vietnamese homozygous major alleles of rs8099917 and rs12979860 are slightly more frequent (83.95% vs. 77,7%) and (79.1% vs. 76.8%) respectively [21]. The Vietnamese homozygous ratio of the major allele at rs8099917 is also higher than Chinese Han ethnicity (80.4%) [22]. Thus, the overall allelic frequencies of SNPs near IL28B gene are not substantially different between Vietnamese populations and the aforementioned Asian ethnicities.

All HCV carriers in the current study were free of the homozygous minor allele at rs8099917 and responded well to the ribavirin interferon combined regimen. Concordant to other studies, the most beneficial medication for HCV carriers holding the T/T major allele of SNP rs8099917 was Peg-INF alpha – ribavirin regimen and was documented [22]. Observations throughout this study also elucidated HCV genotype 1 or 6 are less responsive to the treatment, although most HCV carriers in Vietnam are more responsive than many other ethnicities [23]. A noted finding identified those with the T/G heterozygous allele are at lower risk of being infected with HCV than the T/T or G/G homozygous allele at rs8099917.

In terms of IL28B genotypes in HBV infections, the study of Dunford L. has not yet established the association between IL28B SNPs s12979860 and HBV susceptibility [20], while this study (Table 3) showed IL28B heterozygous SNPs holders have higher resistance against HBV infection. This conclusion is somewhat discordant to what has been inferred from the studies of Vincent Soriano [12] or Kim YJ [11], in which the interleukin-28B (IL-28B) genotype did not seem to have a role in the development of chronic hepatitis B or HBV clearance. Data found in this study also demonstrated that holders of T/G heterozygous allele at SNP rs8099917 are protective against the development of liver cancer. Based on this data, only four out of 262 bearing the G/G minor allele at SNP rs8099917 and one harboring rs12979860 T/T minor allele were in the HBV infected HCC group.

Although homozygous minor allele holders were only observed in HBV infected HCC patients and the frequency of minor C allele holders at SNP rs8099917 were higher among HBV infected HCC patients than those in non-HCC patients with HBV, the sample size was not large enough for statistical calculations to reach significance. Additionally, this did not

Table 4: Allelic frequencies and genotypes of SNPs near IL28B gene between non-HCC patient carrying HBV (NHCCHBV) and HBV-induced HCC patients.

IL28B SNPs	allele	Non-HCC HBV (+) (n=60)	HCC HBV (+) (n=65)	OR (95% CI)	χ^2, p
rs8099917	T G	0.9583 (115) 0.0434 (5)	0.915 (119) 0.085 (11)	1 2.1 (0.65-8.03)	1.92, >0.05
	T/T T/G G/G	55 (91,67) 5 (8.33) 0 (0)	58 (89.23) 3 (4.61) 4 (6.16)	1 1.6 (0.29-10.6) Not applicable	0.37, >0.05 Not applicable
rs12979860	C T	0.9417 (113) 0.0583 (7)	0.938 (122) 0.061 (8)	1 1.05 (0.32-3.5)	0.02, >0.05
	C/C C/T T/T	53 (88.33) 7 (11.67) 0 (0)	58 (89.23) 6 (9.23) 1 (1.54)	1 0.78 (0.2-2.9) Not applicable	0.17, >0.05 Not applicable

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draw a robust conclusion that the C minor allele at IL28B SNP rs8099917 was a risk factor involving the progression of chronic HBV carriers into HCC. This is similar to what has been inferred from a previous study of Pierluigi Toniutto or Kaneko S., where the authors revealed an increased risk of IL-28B rs12979860 T or rs8099917 C minor alleles in chronic HBV patients developing into liver cancer [24,25].

Conclusion

While heterozygous IL28B genotypes were found to protect the ethnic Vietnamese against HBV/HCV infection, holders of the heterozygous T/C SNP rs8099917 allele had a lower risk of HCC development.

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Authors' Contributions

LHS raised the idea, performed statistical analysis, revised the project and corrected the manuscript. NTT designed the study and wrote the manuscript. DPG and DTQ provided daily supplies for the project. VMT, MTB, and NLT collected the biopsies and controlled patient information.

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