Correlation between the genetic variations in interleukin 28B and chronic hepatitis C virus genotypes in the Chinese population

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Received August 6, 2013; Accepted March 5, 2014

DOI: 10.3892/mmr.2014.2242

Abstract. Genetic variations at the interleukin 28B (IL-28B) locus and chronic hepatitis C virus (HCV) genotypes are significant factors in predicting the therapeutic outcome for HCV infection. The present study aimed to determine the geographical distribution of HCV genotypes and single nucleotide polymorphisms (SNPs) associated with IL-28B in Chinese patients infected with HCV. The gene frequencies of 13 types of IL-28B SNPs and HCV genotypes were investigated in 1,014 patients infected with HCV, who were recruited from varying regions of China. The correlation between the SNPs of IL-28B, the HCV genotypes and age, gender and geographical location were investigated. The data revealed geographical differences in age, gender and HCV genotypes in the Chinese HCV patients. HCV genotype 1 was distributed extensively and had a higher incidence compared with other HCV genotypes in all regions, with the exception of South (38%) and Northwest China (45.6%). A gender differences also existed (P<0.01). The distribution of genotype 6 was lower compared with other HCV genotypes in the majority of the regions (P<0.01). In middle-aged patients, the number of male patients was higher than the number of female patients in North and South China, which was the opposite of the results found in the other regions. There were no geographical differences in IL-28B SNPs in Chinese HCV-infected populations. Notably, there were significant differences between HCV genotype 1 and 2 in the genotype percentages of the majority of SNPs (P<0.01). In conclusion, a geographical distribution in HCV genotypes and a correlation between HCV genotypes and IL-28B SNPs have been identified, and indicate that these variants may be associated with spontaneous and treatment-induced HCV clearance.

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Key words: chronic hepatitis C virus, genotype, single nucleotide polymorphisms, interleukin 28B, Chinese population

Introduction

Hepatitis C is currently the dominant cause of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). It is estimated that ~170 million individuals worldwide are infected with HCV, with a global prevalence of ~3% (1,2). In total, there are >3.5 million new cases of hepatitis C virus (HCV) infection per year (3). In China, there are ~38 million individuals who are infected with HCV, with a prevalence of ~3.2%. Endemic strains of HCV have been identified that persist in specific locations (4). There are 11 HCV genotypes with >70 subtypes, among which, four HCV genotypes (genotypes 1, 2, 3 and 6) are prevalent in the Chinese population (5). The distribution of HCV genotypes is significantly regional. HCV genotype 1 is globally spread, and found particularly within Europe and North America (6). Genotype 2 is located in West Africa, while genotype 6 is found in South East Asia (7). Recently, genotype 3A has been found to dominantly infect intravenous drug-user populations in Europe (4). However, the geographical distribution of HCV genotypes in the Chinese population has rarely been investigated.

An acute HCV infection can induce host innate and adaptive immune responses (8,9). In total, 15-25% of HCV-infected patients successfully eliminate the virus, whereas the majority of patients develop chronic liver disease, cirrhosis and HCC (10).

Various host factors can affect treatment-induced control and the spontaneous clearance of HCV infection. HCV clearance is associated with polymorphisms in the region of the interleukin-28B (IL-28B) gene, which indicates that interferon (IFN)-λ3, the gene product, is vital in the immune response to HCV (11). Spontaneous HCV clearance occurs in 15-25% of cases (12), which may be affected by a number of factors, including gender, ethnicity, jaundice and co-infections. Numerous studies have demonstrated that host genetic polymorphisms may lead to differences in host immune function and therefore affect the clinical outcome of HCV infection. Host genetic variation in the IL-28B gene was shown to markedly predict viral clearance and sustained virological response (SVR) rates in patients with HCV infection (13-15). The region on chromosome 19 that is associated with HCV treatment response contains multiple single nucleotide polymorphisms (SNPs) in linkage disequilibrium around the IL-28B gene (16-18) In the past years, genetic studies have identified several SNPs in and near IL-28B that are associated with viral clearance. Sequence analysis of the

Table I. Regional information of patients infected with HCV in China.

Regions of China	Hospital	No. of patients
North	Peking University People's Hospital	59
	Beijing Friendship Hospital	33
Northeast	Shengjing Hospital of China Medical Hospital	34
	The First Hospital of Jilin University	34
	The Second Affiliated Hospital of Haerbin Medical University	21
Southwest	West China Hospital, Suchuan	22
	The First Affiliated Hospital of Kunming Medical College	40
	Southwest Hospital	29
South	The First Affiliated Hospital of Guangxi Medical University	40
	Nanfang Hopital	14
	The Third Affiliated Hospital of Sun Yat-sen University	50
Central	Henan Provincial People's Hospital	95
	The First Affiliated Hospital of Zhengzhou University	28
	People's Hospital of Hubei Wuhan University	38
	Affiliated Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology	32
	The Second Xiangya Hospital of Central South University	31
Northwest	Tangdu Hospital	40
	The First Affiliated Hospital of Shanxi Medical University	37
	The First Affiliated Hospital of Lanzhou University	58
	Ningxia People's Hospital	27
East	The First Affiliated Hospital of Nanchang University	37
	The First Affiliated Hospital of Anhui Medical University	19
	The Second Hospital of Shangdong University	41
	The First Affiliated Hospital of Medical College Zhejiang University	33
	The First Affiliated Hospital of Fujian Medical University	11
	Shanghai Ruijin Hospital	52
	The First Affiliated People's Hospital of Shanghai Jiaotong University	2
	Jiangsu Province Hospital	57

HCV, hepatitis C virus.

IL-28B region indicated two SNPs (rs8103142 and rs28416813) as candidate causal variants (16), but little is known about other SNPs associated with IL-28B. Two good responder alleles, rs12979860 and rs8099917, have been found to be associated with natural viral clearance and low levels of mRNA IL-28B in peripheral mononuclear cells (17,18). However, IL-28B gene expression in liver samples appears not to be regulated by the IL-28B genotypes, and studies on the association between IFN-λ mRNA and IL-28B genotypes lead to conflicting results. Therefore, there is an urgent requirement to clarify detailed epidemiological information with regard to the SNPs of IL-28B correlated with the future prospects and treatment of HCV patients. Furthermore, the current data on other SNPs in IL-28B are poorly understood and require further study.

The aim of the present study was to analyze the epidemiology of Chinese hepatitis C patients through i) the host genotypes and SNPs associated with IL-28B, ii) the HCV genotypes in different regions and iii) the possible association between IL-28B-related genetic variations and HCV genotypes in hepatitis C.

Patients and methods

Patients population. A total of 1,014 patients infected with HCV (554 males and 460 females; mean age, 45 years) were randomly recruited from 28 hospitals in varying regions in China (Table I). The registration ID of the present study is NCT01293279 (www.clinicaltrials.gov). The study was approved by the ethical committees of all the hospitals that patients were recruited from in the present study. Written informed consent was obtained from each patient. All the patients had been confirmed as positive for anti-HCV antibody and serum-HCV RNA. All the hospitals were divided territorially into North, Northeast, Southwest, South, Central, Northwest and East China (Fig. 1) (19). The study included 92 patients infected with HCV in North China, 91 in the Southwest, 104 in the South, 224 in Central China, 162 in the Northwest, 252 in the East and 89 in the Northeast. All the patients with HCV infection did not receive any treatment, and the age, gender and regions were taken into consideration.

Figure 1. Regional distribution of HCV patients recruited. In total, 28 hospitals were divided territorially into North, Northeast, Southwest, South, Central, Northwest and East China. The study included 92 HCV-infected patients in North China, 91 in the Southwest, 104 in the South, 224 in Central China, 162 in the Northwest, 252 in the East and 89 in the Northeast (19). HCV, hepatitis C virus.

Genomic DNA and RNA extraction. Genomic DNA and total RNA from liver biopsies were extracted using the Qiagen RNeasy Mini kit (Qiagen, Inc., Valencia, CA, USA) (20).

HCV genotyping. HCV genotyping was conducted using the INNO-LiPA HCV II assay (Innogenetics, Zwijnaarde, Belgium), which is based on hybridization of probes with the 5' non-coding region of HCV. According to the HCV gene sequences published in GenBank (AF333324, D16435, KF035127 and KC844040), the HCV 5' non-coding region (nt299-1) was selected, and one pair of specific primers were designed for nested polymerase chain reaction (PCR). The sequences of the PCR primers were as follows: Sense: -299 5'-CCCTGTGAGGAACTWCTGTCTTCACGC-3' (-299~-273); and antisense: 5'-GGTGCACGGTCTACGAGACCT-3' (-1~-21) (W is A or T). The probes used for the detection of the different serum types are also listed as follows: Genotype 1: -170 AATTGCCAGGACGACC; genotype 2: -83 TAGCGT TGGGTTGCGA; genotype 3: -170 AATCGCTGGGGTG ACC; and genotype 6: -81 AGTAGCGTTGGGTTGC. The HCV 5' non-coding region of the HCV genome was amplified using nested PCR. Briefly, 5 μl cDNA was amplified for >40 cycles in a total volume of 50 μl, each consisting of 1 min at 95˚C, 1 min at 55˚C and 1 min at 72˚C. From the second round of amplification, 1 μl product was amplified again with the same primers for another 40 cycles. The nested PCR products were subjected to electrophoresis in a 2% agarose gel. The probes specific for the different types of HCV were added with a poly(dT) tail at their 3' end. Primer (20 pmol) was incubated for 1 h at 37˚C in 25 μl buffer (3.2 mM-dTTP, 25 mM-Tris-HC1 pH 7.5, 0.1 M-sodium cacodylate, 1 mM-$CoCl_2$, 0.1 M-dithiothreitol and 60 U terminal deoxynucleotidyl transferase). The reaction was stopped by adding 2.5 μl EDTA (0.5 M, pH 8.0) and diluted with 20X SSC. This solution was applied on a nitrocellulose membrane, and was fixed to the membrane by baking at 80˚C for 2 h, and then was hybridized with equal volumes of the nested PCR products.

Assay for HCV RNA. Serum was obtained from the HCV-infected patients, and the total RNA was isolated using an RNeasy Mini kit and RNase-Free DNase Set (Qiagen, Hilden, Germany). The HCV RNA content was detected by Abbott RealTime HCV (Abbott Laboratories, Des Plaines, IL, USA).

IL-28B genotyping. Genotyping for the IL-28B gene was performed by the iPLEX system [MassARRAY® Real-Time Transactional Memory (RTTM) software for SNP genotyping; iPLEX Gold; Sequenom, San Diego, CA, USA]. The DNA was blind coded and tested using a 384-SpectroCHIP® microarray (Sequenom). A matrix-assisted laser desorption/ionization time-of-flight mass spectrometer was used for data acquisitions from the SpectroCHIP microarray. The results were analyzed using Sequenom MassARRAY RTTM software. The region on around the IL-28B gene on chromosome 19 contains multiple SNPs in linkage disequilibrium. The present study focused on the genotyping of thirteen SNPs associated with IL-28B: rs8013142, rs28416813, rs10853728, rs7248668, rs8105790, rs11881222, rs12979860, rs12980275, rs4803219, rs8099917, rs8109886, rs4803223 and rs10853727.

Statistical analysis. The Hardy-Weinberg disequilibrium test was performed for each SNP genotype associated with IL-28B. The gene frequencies were compared between groups using the χ^2 test with Yates correction or Fisher's exact test. Group means were presented as the mean ± standard deviation, and were compared by analysis of variance and Student's t-test.

Table II. Gender differences in HCV patients of different ages and regions in China.

	Age, %			
Regions and gender	Old-aged adults	Middle-age adults	Young adults	The young
North	12.09	24.18	17.58	1.10
Male	18.68	17.58	8.79	0.00
Female				
Northeast				
Male	8.99	19.10	19.10	0.00
Female	10.11	24.72[a]	17.98	0.00
Southwest				
Male	4.49	7.87	46.07	0.00
Female	5.62	11.24[a]	24.72	0.00
South				
Male	3.85	13.46	47.12	0.00
Female	6.73	11.54	17.31	0.00
Central				
Male	4.02	12.50	30.36	0.00
Female	3.57	29.91[a]	19.64	0.00
Northwest				
Male	5.56	17.90	38.27	0.00
Female	4.94	20.37	12.96	0.00
East				
Male	10.71	17.46	25.79	0.40
Female	9.13	24.21[a]	12.30	0.00

[a]Significant differences from the male group of the same region (P<0.01). HCV, hepatitis C virus.

The serum HCV RNA levels were expressed as the original values. The HCV RNA levels were divided into high, medium and low level groups. The statistical analyses were performed with the SPSS 12.0 statistical package (SPSS, Inc., Chicago, IL, USA). All statistical analyses were based on two-sided hypothesis tests, with P<0.05 used to indicate a statistically significant difference.

Results

Baseline characteristics. A total of 1,014 HCV-infected patients were randomly recruited from 28 hospitals in the 7 regions of China for the present study (Fig. 1 and Table I). The overall gender ratio of male to female was 1.204 (554/460). The HCV-infected population was divided according to their age into four groups: The old-aged adults (>60 years old), the middle-aged adults (45-59 years old), the young adults (18-44 years old) and the young (<18 years old). HCV genotypes 1, 2, 3 and 6 were included in the study. Furthermore, HCV RNA expression was detected and divided into high (RNA≥$1x10^7$), medium ($1x10^5$≤RNA<$1x10^7$) and low (RNA<$1x10^5$) expression.

Geographical distribution of HCV genotypes. The HCV genotypes in Chinese patients were investigated. The data revealed that HCV genotype 1 was distributed more extensively compared with other genotypes in all regions, with the exception of South and Northwest China (P<0.01). In South China, the distribution of HCV genotypes 1 and 3 was higher compared with other genotypes, with percentages of 38 and 37%, respectively. The percentages of HCV genotypes 1 and 2 in the Northwest region were 45.6 and 41%, respectively. In all regions, with the exception of Southwest (15%) and South (17%) China, the percentage of genotype 6 was recorded to be the lowest, (Fig. 2).

Distribution of HCV-infected patients in different genders and ages in China. In all the recruited HCV-infected patients, the old-aged adults, middle-aged adults, young adults and the young accounted for 14.8 (150/1,014), 37.7 (382/1,014), 47.3 (480/1,014) and 0.2% (2/1,014) of cases, respectively. The patients with compensated and decompensated cirrhosis accounted for 8.8 (89/1,014) and 5.3% (54/1,014) of the cases, respectively (Fig. 3). The old-aged, middle-aged and young adults accounted for 27, 60 and 13% of cases, respectively, in the compensated cirrhosis group, and for 28, 57 and 15% of cases, respectively, in the decompensated cirrhosis group (Fig. 3). The distribution of the young in the purely HCV-infected patients was significantly higher compared with that in the compensated and decompensated cirrhosis groups. However, in the compensated and decompensated cirrhosis groups, the distribution rate of the middle-aged adults was higher than the other groups (P<0.01).

Table III. Gender difference of geographical HCV genotypes in China.

Regions and gender	HCV genotypes, %			
	1	2	3	6
North				
Male	55.00	31.58	100.00[a]	0.00
Female	45.00	68.42[a]	0.00	0.00
Northeast				
Male	45.65	54.84	33.33	50.00
Female	54.35	45.16	66.67	50.00
Southwest				
Male	52.94	62.50	66.67	53.85
Female	47.06	37.50[a]	33.33	46.15
South				
Male	62.00[a]	50.00	81.82	76.00
Female	38.00	50.00	18.18	24.00[a]
Central				
Male	44.93	46.43	75.00	55.56[a]
Female	55.07[a]	53.57	25.00	44.44
Northwest				
Male	56.16[a]	56.06	100.00	100.00
Female	43.84	43.94	0.00	0.00
East				
Male	55.43[a]	47.75	75.00	44.44
Female	44.57	52.25	25.00	55.56

[a]Significant differences from the male group of the same region and HCV genotypes (P<0.01). HCV, chronic hepatitis C virus.

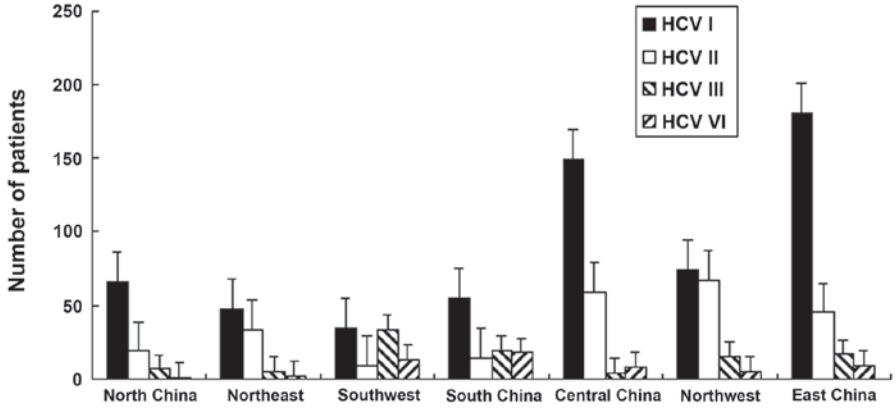

Figure 2. Geographical distribution of HCV genotypes 1, 2, 3 and 6 in different regions of China. The number of HCV-infected patients with different genotypes is plotted against the different regions of China, with data for genotypes 1-4. HCV, hepatitis C virus.

In the middle-aged adults group, the number of male patients was higher compared with the number of females in North and South China, which was the opposite of the results found in the other regions. In particular, in Eastern China, the number of female patients was significantly higher compared with the number of males (P<0.01). However, in the young adult group, there were far more males compared with females in the majority of the regions, with the exception of North China (P<0.01) (Table II).

Gender differences of HCV genotypes in the varying regions. In all regions, no gender difference was found in HCV genotype 1 (P<0.05). However, in HCV genotype 2, there were significantly less males compared with females in North and Southwest China (P<0.01). In HCV genotype 3, the males were extensively distributed in all the regions, with the exception of the Northeast. In HCV genotype 6, the infected rate in males was significantly higher than that in females in South China (P<0.01) (Table III).

Table IV. Distribution of SNP genotypes associated with IL-28B in HCV genotypes 1 and 2.

SNPs	HCV infected	HCV genotype 1	HCV genotype 2
rs8013142, % (n)			
C/T	98.13 (995)[a]	99.66 (587)	99.23 (258)
T/T	0.20 (2)	0.00 (0)	0.38 (1)
C/C	1.67 (17)	0.34 (2)	0.38 (1)
Gene frequency, %			
T:C	49/51	50/50	50/50
rs28416813, % (n)			
G/C	77.71 (788)[a]	79.80 (470)	88.46 (230)[b]
G/G	22.29 (226)	20.20 (119)	11.54 (30)
Gene frequency, %			
G:C	62/38	60/40	58/42
rs10853728, % (n)			
C/G	30.47 (309)	34.63 (204)	27.69 (72)
G/G	3.46 (35)	3.06 (18)	3.85 (10)
C/C	66.07 (670)[a]	62.31 (367)	68.46 (178)[b]
Gene frequency, %			
G:C	19/81	20/80	18/82
rs7248668, % (n)			
G/A	14.60 (148)	17.66 (104)	11.15 (29)
G/G	85.21 (864)[a]	82.17 (484)	88.46 (230)[b]
A/A	0.20 (2)	0.17 (1)	0.38 (1)
Gene frequency, %			
G:A	93/7	91/7	94/6
rs8105790, % (n)			
T/C	28.4 (288)	33.62 (198)	22.31 (58)
T/T	71.4 (724)[a]	66.38 (391)	76.54 (200)[b]
C/C	0.2 (2)	0.00 (0)	0.77 (2)
Gene frequency, %			
T:C	86/14	83/17	88/12
rs11881222, % (n)			
G/A	16.17 (16)	19.86 (117)	10.77 (28)
A/A	83.73 (849)[a]	80.14 (472)	88.46 (230)[b]
G/G	0.20 (2)	0.00 (0)	0.77 (2)
Gene frequency, %			
G:A	8/92	10/90	6/94
rs12979860, % (n)			
C/T	15.09 (153)	18.17 (107)	11.15 (29)
C/C	84.71 (859)[a]	81.66 (481)	88.46 (230)[b]
T/T	0.20 (2)	0.17 (1)	0.38 (1)
Gene frequency, %			
T:C	8/92	9/91	6/94
rs12980275, % (n)			
G/A	15.68 (159)	19.52 (115)	10.77 (28)
G/G	2.96 (30)	0.00 (0)	1.15 (3)
A/A	81.36 (825)	80.48 (474)	88.08 (229)[b]
Gene frequency, %			
G:A	11/89	10/90	7/93

Table IV. Continued.

SNPs	HCV infected	HCV genotype 1	HCV genotype 2
rs4803219, % (n)			
C/T	15.68 (159)	19.86 (117)	11.54 (30)
C/C	84.32 (855)[a]	80.14 (472)	88.46 (230)[b]
Gene frequency, %			
T:C	8/92	10/90	6/94
rs8099917, % (n)			
G/T	14.40 (146)	17.83 (105)	11.60 (29)
T/T	85.40 (866)[a]	82.00 (483)	88.00 (220)
G/G	0.20 (2)	0.17 (1)	0.40 (1)
Gene frequency, %			
G:T	7/93	9/91	6/94
rs8109886, % (n)			
C/A	18.24 (185)	21.73 (128)	15.77 (41)
C/C	81.56 (827)[a]	78.10 (460)	83.85 (218)[b]
A/A	2.00 (2)	0.17 (1)	0.38 (1)
Gene frequency, %			
C:A	91/9	89/11	92/8
rs4803223, % (n)			
G/A	15.38 (156)	18.17 (107)	11.92 (31)
A/A	84.32 (855)[a]	81.83 (482)	88.08 (229)[b]
G/G	0.30 (3)	0.00 (0)	0.00 (0)
Gene frequency, %			
G:A	8/92	9/91	6/94
rs10853727, % (n)			
T/C	1.48 (15)	1.36 (8)	0.00 (0)
T/T	98.52 (999)[a]	98.64 (581)	100.00 (260)
Gene frequency, %			
T:C	99/1	99/1	100/0

[a]Significant differences from the other two allelic genes of the same SNP; [b]Significant differences in genotype percentages compared with HCV genotype 1 (P <0.01). SNP, single nucleotide polymorphism; IL-28B, interleukin 28B; HCV, hepatitis C virus.

HCV RNA expression among HCV genotypes. The HCV RNA in all the genotypes was highly expressed, with the exception of genotype 1b+2. There was no difference in HCV RNA expression among HCV genotypes 1, 2 and 3. However, the number of patients with high RNA expression in genotype 6 was significantly higher compared with that in the other genotypes (P<0.01). In genotype 1b+2 patients, the number of patients with high RNA expression was lower compared with the patients with medium and low levels of RNA expression, but no statistical significance was found due to the small number of specimens (Fig. 4).

Distribution of SNPs associated with IL-28B. A total of 13 SNPs associated with IL-28B (rs8013142, rs28416813, rs10853728, rs7248668, rs8105790, rs11881222, rs12979860, rs12980275, rs4803219, rs8099917, rs8109886, rs4803223 and rs10853727) were investigated in 1,014 HCV-infected

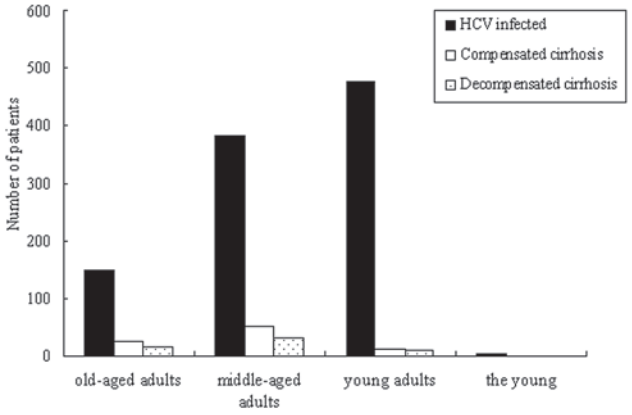

Figure 3. Age distribution of HCV-infected patients and those with related complications. The number of HCV-infected patients is plotted against the different age groups, including the old-aged adults (>60 years old), the middle-age adults (45-59 years old), the young adults (18-44 years old) and the young (<18 years old). HCV, hepatitis C virus.

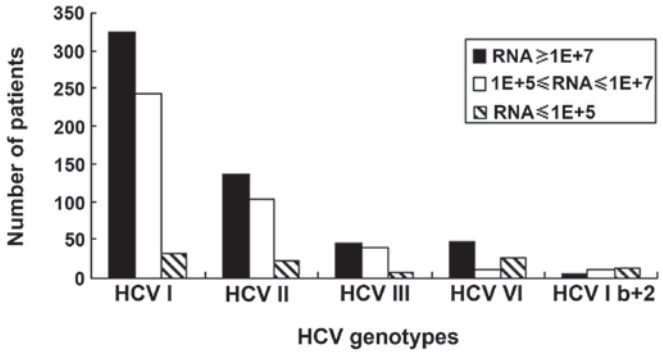

Figure 4. HCV RNA expression among the different HCV genotypes. The number of HCV-infected patients is plotted against the different HCV genotypes with high (RNA≥1x10^7), medium (1x10^5≤RNA<1x10^7) and low (RNA<1x10^5) levels of HCV RNA expression. HCV, hepatitis C virus.

patients in the present study. The distribution of host genotypes in each SNP were detected (Table IV). The data show that the percentage of genotype C/T in rs8013142 (98.13%), G/C in rs28416813 (77.71%), C/C in rs10853728, rs12979860, rs4803129 and rs8109886 (66.07, 84.71, 84.32 and 81.56%, respectively), G/G in rs7248668 (85.21%), T/T in rs8105790, rs8099917 and rs10853727 (71.40, 85.40 and 98.52%, respectively), and A/A in rs11881222, rs12980275 and rs4803223 (83.73, 81.36 and 84.32%, respectively) were significantly higher compared with the other two allelic genes. Notably, there were significant differences in the genotype percentages of all SNPs between HCV genotypes 1 and 2 in the majority of SNPs (with the exception of rs8013142, rs8099917, rs8109886 and rs10853727). Genotypes rs28416813 (C/C), rs4803219 (T/T) and rs10853727 (C/C) were not found in any of the recruited HCV patients (Table IV).

Overall, no geographical differences in SNPs existed in the Chinese HCV-infected population. However, SPSS analysis revealed that several correlations exist between the SNPs genotypes and HCV (P<0.01).

Discussion

As a major cause of chronic liver disease globally, the prevalence of HCV infection exhibits significant geographical variations. Distinct epidemiological characteristics and differences in methodologies are reflected by these variations. Therefore, in the present study, all HCV samples, originally obtained from 28 different hospitals around China, were analyzed in the same center.

The geographical differences in HCV genotypes have long since been discovered, and underlie variations when conducting epidemiological surveys, etiological diagnoses, clinical treatment and vaccine development in a specific region (21). For example, the HCV genotype 1 is predominant in Japan and South Asia. Genotype 2 is prevalent in Taiwan and genotypes 1, 2 and 6 are prevalent in Thailand. The prevalence of genotype 3 is higher in Europe compared with Africa and Asia (22).

In the present study, HCV genotype 1b was shown to be extensively distributed in North (71.8), Northeast (53.9), South (52), Central (66.5) and East (71.8%) China. HCV genotypes 1b and 3 were the main genotypes in Southwest China. HCV genotypes 1b and 2a were the prevalent genotypes in Northeast China. The geographical distribution of HCV genotypes has been investigated by a variety of studies in China, however the results are paradoxical. A number of studies show that HCV genotype 1b is the most widely distributed genotype (23), and is most predominant in the North (Beijing, 56.8%), East (Shanghai, 69.1%) and Southwest (Chongqing, 32.9%), while genotype 2a is most predominant in the Northwest (Wuwei, 59.1%) (24-27). The differences in the distribution of HCV genotypes may arise from the varying detection methods and small sample size used among the literature. HCV genotype 6 was relatively uncommon throughout all regions, while in the Southwest it is the most predominant (Yunnan Province, 47%) (28). In the present study, the distribution of HCV genotypes varied and demonstrated geographical properties in China. HCV genotype distribution may be caused by a source of infection, presence of ethnic groups and individual differences. However, the mechanism of HCV genotype variation and the relevance with host genovariation remain unknown and require further investigation.

HCV genotypes are considered to be a major determinant of the response to treatment in HCV infection (29,30). Furthermore, increasing studies clearly indicate that host genetics are also critical factors affecting the response to treatment (31). HCV clearance is associated with polymorphisms in the IL-28B gene region, indicating a vital role for the IFN-λ3 gene product in the immune response to HCV (11). The present study initially investigated 13 SNPs associated with IL-28B in a range of regions and HCV genotypes in the Chinese population. It has previously been clarified that host genetics play an essential role in clearing acute hepatitis C infection and achieving an SVR (32). Variants in the minor alleles, rs8099917 and rs12979860, are associated with SVR and natural viral clearance (33). In the present study of Chinese HCV-infected populations, the rate of T/T in rs8099917 and C/C in rs12979860 was significantly higher compared with the other two allelic genes (P<0.01) and was correlated with HCV genotype variation. Other SNPs associated with IL-28B were also investigated in the present study. Notably, the genotype percentages of all the SNPs were significantly different between HCV genotypes 1 and 2, with the exception of rs8013142, rs8099917, rs8109886 and rs10853727. The SPSS analysis data revealed that there was significant relevance between the host and HCV genotypes (P<0.01). This indicated that a certain number of interactions were occurring between the host and HCV genotypes in the Chinese HCV-infected population. The molecular mechanism of these associations require elucidating in further studies. The present study found that these susceptible SNPs correlated with HCV infection, which may be useful for use in epidemiological surveys and etiological diagnoses of HCV infection.

In conclusion, the present study investigated the geographical distribution of HCV genotypes and SNPs associated with IL-28B in Chinese patients infected with HCV, and found a geographical distribution in the HCV genotypes, and a correlation between HCV genotypes and several IL-28B SNPs. The study indicated that these variants may be associated with spontaneous and treatment-induced HCV clearance.

Acknowledgements

This study was supported by grants from the National Science and Technology Major Project for Infectious Disease Control during the 11th Five-Year Plan Period (grant nos. 2008ZX10002-012 and 2008ZX10002-013) and the 12th Five-Year Plan Period (grant no. 2012ZX10002003), and by grants from the Natural Science Foundation of Gansu Province (grant no. 0803RJZA057), Fundamental Research Funds for the Central Universities (lzujbky-2009-150) and Bristol-Myers Squibb. Operational support and statistical analyses were provided by Research Pharmaceutical Services, Beijing, China.

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