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ORIGINAL RESEARCH

Association of *IFNL3* rs12979860 polymorphism with HCV-related hepatocellular carcinoma susceptibility in a Chinese population

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Background: The association between interferon lambda-3 (*IFNL3*, also known as interleukin 28B, *IL28B*) rs12979860 polymorphism and the development of hepatocellular carcinoma (HCC) has been investigated in recent studies with inconclusive and inconsistent results. *IFNL3* rs12979860 polymorphism has been shown a marked differential distribution with regional and ethnic variation. Whether this single nucleotide polymorphism influences susceptibility to hepatitis C virus (HCV)-related HCC remains elusive.

Methods: In this case–control study, a total of 157 Chinese Han patients with chronic HCV infection were enrolled, including 62 HCV-related HCC patients and 95 chronic hepatitis C (CHC) patients without HCC, and the genetic polymorphism of *IFNL3* rs12979860 was genotyped via a DNA microarray-based assay. The logistic regression analysis was employed to determine the correlation between the genetic polymorphism and risk of HCV-related HCC.

Results: A higher proportion of CT/TT genotype and T allele was observed in HCC patients compared to the CHC group. Under the genetic model of allele frequency, the T allele was associated with elevated risk of HCV-related HCC in the Chinese population compared to C allele after an adjustment for age, gender, body mass index, HCV infection duration, and HCV genotypes (P=0.046). In the subgroup analysis stratified by HCV genotype, subjects with CHC genotype 1b infection carrying rs12979860 T allele and CT+TT genotype had higher susceptibility to HCC than those with C allele and CC genotype (P=0.020, P=0.037, respectively).

Conclusion: *IFNL3* rs12979860 polymorphism with T allele could be a factor that increases the risk of HCV-related HCC in the Chinese population, especially those subjects with CHC genotype 1b infection.

Keywords: *IFNL3*, rs12979860, polymorphism, HCV, HCC

Introduction

Hepatitis C virus (HCV) infection is a major public health problem throughout the world. Chronic HCV infection may eventually progress to liver cirrhosis (LC) or even develop to hepatocellular carcinoma (HCC).[1,2] The risk of development from chronic hepatitis C (CHC) to HCC involves a complex interplay between the viral and host genetic factors.[3] Our previous study[4] together with others' have revealed that host gene polymorphisms may play important roles in the development and progression of HCV-related HCC.

IFNL3 encodes IFN lambda-3 (IFN-λ3), also known as interleukin 28B, which belongs to the type III IFN-λ family consisting of IL29/IFNL1, IL28A/IFNL2, IL28B/IFNL3, and newly discovered IFNL4.[5–7] It has been investigated that

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rs12979860 (C/T), located near the *IFNL3* gene, involves in a number of aspects of HCV infection and disease progress,[8–19] including response to therapy, natural elimination of the virus, viral clearance rate, changes in gene expression and lipid metabolism, hepatocyte death rate, inflammatory activity, fibrosis risk, cirrhosis and hepatocarcinogenesis.

Several studies have been recently carried out to explore the association between *IFNL3* rs12979860 polymorphism and HCC risk in different geographic regions and ethnic populations, but with inconclusive and inconsistent results (Table 1).[20–36] Some reports demonstrated that the carriage of T allele was a risk factor for HCC development.[20–29] In contrast, one study showed opposite results,[30] while other studies did not find any significant association between *IFNL3* rs12979860 polymorphism and HCC risk.[31–36] Therefore, we sought to conduct a case–control study to investigate the role of genetic polymorphism of *IFNL3* rs12979860 in the susceptibility to HCV-related HCC in a Chinese population.

Materials and methods

Patients

A total of 157 patients with chronic HCV infection, including 62 HCV-related HCC patients, and 95 HCV-infected patients without HCC as the control subjects, were recruited from Tianjin Second People's Hospital and Tianjin institute of Hepatology from July 2015 to February 2017. The diagnostic criteria for CHC with or without HCC were based on the combination of clinical history, physical examination, imaging, and laboratory data, and/or histology. Seropositive patients for other hepatitis viruses such as hepatitis B virus or human immunodeficiency virus were excluded from this study. The written informed consent and the ethical approval for this study were obtained from all subjects and the Faculty of Health Science Ethics Committee of Tianjin Second People's Hospital. The following data were collected from all HCC patients and control subjects including gender, age, body mass index (BMI), the known duration of HCV infection, and infected HCV genotype.

Genotyping

Genotyping for rs12979860 polymorphism was performed via a DNA microarray-based assay, as described in our previous study.[37]

Statistical analysis

All analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Chi-square test and Student *t*-test were used where appropriate. The logistic regression analysis was employed to analyze the correlation between the genetic polymorphism and risk of HCC. A *P*-value of less than 0.05 was considered to indicate a significant difference.

Table 1 Characteristics of previous studies on the association of *IFNL3* rs12979860 polymorphism and HCC risk

Study	Year	HCV genotype	Risk factor associated with HCC	Reference
Buivydiene et al.	2018	GT1 GT2 GT3	rs12979860 CC genotype	30
Suo et al.	2013	ND	rs12979860 TT genotype	20
Attallah et al.	2018	GT4	rs12979860 TT genotype	21
Chang et al.	2015	GT1 non-GT1	rs12979860 CT+TT genotype	22
Lee et al.	2015	GT1 non-GT1	rs12979860 CT+TT genotype	23
Ibrahim et al.	2016	ND	rs12979860 CT+TT genotype	24
Chang et al.	2018	GT1 non-GT1	rs12979860 CT+TT genotype	25
Fabris et al.	2011	ND	rs12979860 T allele	26
El-Awady et al.	2012	GT4a	rs12979860 T allele	27
Eurich et al.	2012	GT1b non-GT1b	rs12979860 T allele	28
Zhang et al.	2016	ND	rs12979860 T allele	29
Agúndez et al.	2012	GT1 non-GT1	No association	31
Bochud et al.	2012	GT1 GT2 GT3 GT4	No association	32
Joshita et al.	2012	GT1 GT2	No association	33
Miura et al.	2012	GT1b	No association	34
Akkiz et al.	2014	ND	No association	35
Zekri et al.	2014	ND	No association	36

Abbreviations: *IFNL3*, interferon lambda-3; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; GT, genotype; ND, not determined.

Results

Demographic and clinical characteristics of the study population

The demographic and clinical characteristics of HCV-related HCC patients and control subjects are reported in Table 2. No significant differences were found between the two groups in terms of gender, age, BMI, duration of HCV infection, and HCV genotype distribution (P>0.05, all).

Genotype and allele frequencies of *IFNL3* rs12979860

The genotype and allele frequencies of *IFNL3* rs12979860 polymorphism are shown in Figure 1. Three genotypes were detected in rs12979860, CC, CT, and TT. The frequencies of these three genotypes were 91.94%, 4.84%, and 3.22% in HCC group (Figure1A), 97.90%, 1.05%, and 1.05% in control group (Figure 1A). The C and T allele frequencies of the two groups were 94.35% and 5.65%, 98.42% and 1.58%, respectively (Figure 1C). Though the distribution of *IFNL3* rs12979860 genotypes and alleles was not statistically different between HCC patients and control subjects (P>0.05), a higher proportion of CT/TT genotype (Figure 1B) and T allele (Figure 1D) was observed in HCC patients.

Table 2 Demographic and clinical characteristics of the study population

Characteristics	HCC patients N=62 (%)	CHC patients N=95 (%)	*P*-value
Gender			0.467
Male	35(56.45%)	48(50.53%)	
Female	27(43.55%)	47(49.47%)	
Age (years)			0.118
≤60	30(48.39%)	58(61.05%)	
>60	32(52.61%)	37(38.95%)	
BMI			0.329
<24	33(53.23%)	43(45.26%)	
≥24	29(46.77%)	52(54.74%)	
Duration of HCV infection (years)			0.825
≤20	25(40.32%)	40(42.11%)	
>20	37(59.68%)	55(57.89%)	
HCV genotype			0.416
1b	51(82.26%)	73(76.84%)	
Non-1b	11(17.74%)	22(23.16%)	

Abbreviations: HCC, hepatocellular carcinoma; CHC, chronic hepatitis C; BMI, body mass index; HCV, hepatitis C virus.

Association analysis of HCV-related HCC risk

We further analyzed the correlation between *IFNL3* rs12979860 polymorphism and susceptibility to HCV-related HCC using logistic regression analysis according to four models (i.e., allele frequency, general genotype, dominant, and recessive models). The OR and P-values of all the genetic models were adjusted on age, gender, BMI, HCV infection duration, and HCV genotypes. Under the genetic model of allele frequency (Figure 2A), the T allele of rs12979860 was associated with elevated risk of HCC compared to the C allele (OR=4.166, 95% CI: 1.024–16.959; P=0.046). Under the dominant model (Figure 2C), the CT+TT genotype increased the risk of developing HCC with a tendency toward statistical significance (OR=4.643, 95% CI: 0.826–26.098; P=0.081). No statistical significances were found under genetic model of general genotype (Figure 2B) as well as recessive model (Figure 2D).

Furthermore, to explore whether HCV genotype would play a role in the association, we separated all the subjects of this study into HCV genotype 1b and non-1b groups (Figure 3). We found that rs12979860 T allele and CT+TT genotype were associated with elevated risk of HCC compared to C allele and CC genotype in HCV 1b genotype group (P=0.020; P=0.037, respectively).

Discussion

In this case–control study, we attempted to investigate the association between *IFNL3* rs12979860 polymorphism and the HCV-related HCC in a Chinese population. As a result, we found a higher proportion of CT/TT genotype and T allele in HCC patients compared to the CHC group. The T allele was associated with elevated risk of HCV-related HCC compared to C allele under the genetic model of allele frequency. In the subgroup analysis stratified by HCV genotype, subjects with CHC genotype 1b infection carrying rs12979860 T allele and CT+TT genotype had higher susceptibility to HCC than those with C allele and CC genotype.

Our data add new insights into the association between genetic polymorphism of *IFNL3* rs12979860 and the susceptibility to HCV-related HCC, and provide further evidence in a Chinese population. Our findings are consistent with the previous observations,[20–29] whereas different from some other reports.[30–36] The following factors might account for the inconsistent results: 1) geographic and racial differences, 2) diversity of viral genotypes.

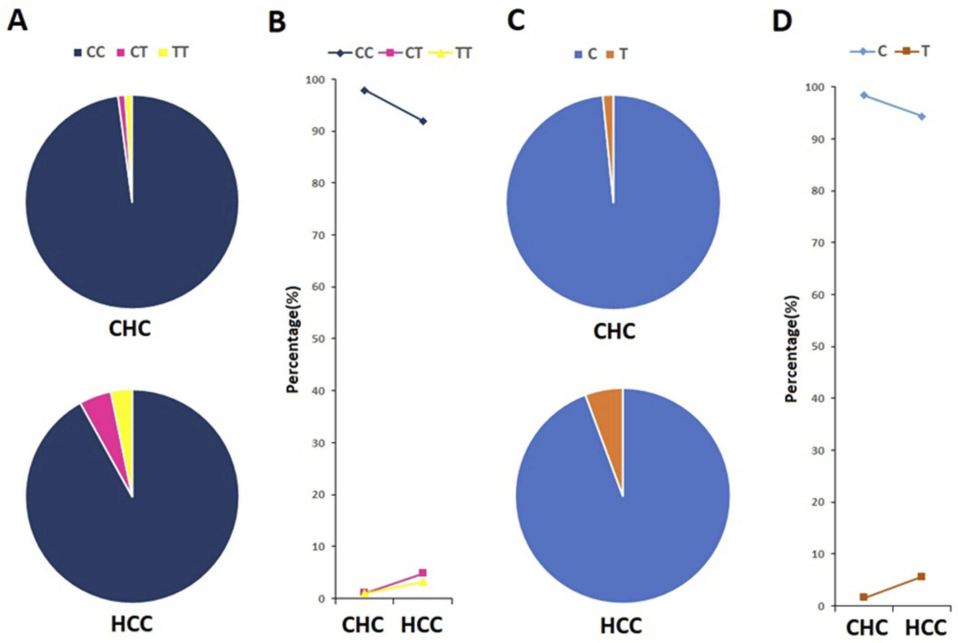

Figure 1 Genotype and allele frequencies of *IFNL3* rs12979860 in CHC and HCC groups.
Notes: (**A**) Genotype frequencies of *IFNL3* rs12979860 in CHC and HCC groups; (**B**) comparison of genotype proportions between CHC group and HCC group; (**C**) allele frequencies of *IFNL3* rs12979860 in CHC and HCC groups; (**D**) comparison of allele proportions between CHC group and HCC group.
Abbreviations: CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; IFNL3, interferon lambda-3.

IFNL3 encodes IFN-λ3, one of the type III IFN-λ family member, inducing signaling through binding to the specific IFN-λ receptor chain 1 and the shared IL-10 receptor chain 2. Accumulating evidence strongly suggests that IFN-λ plays a major role in the control of viral infection and antitumor activity,[38–40] including activation immune cells and suppression of HCC cell proliferation and growth in HCC models.[41,42] The allelic variants of the

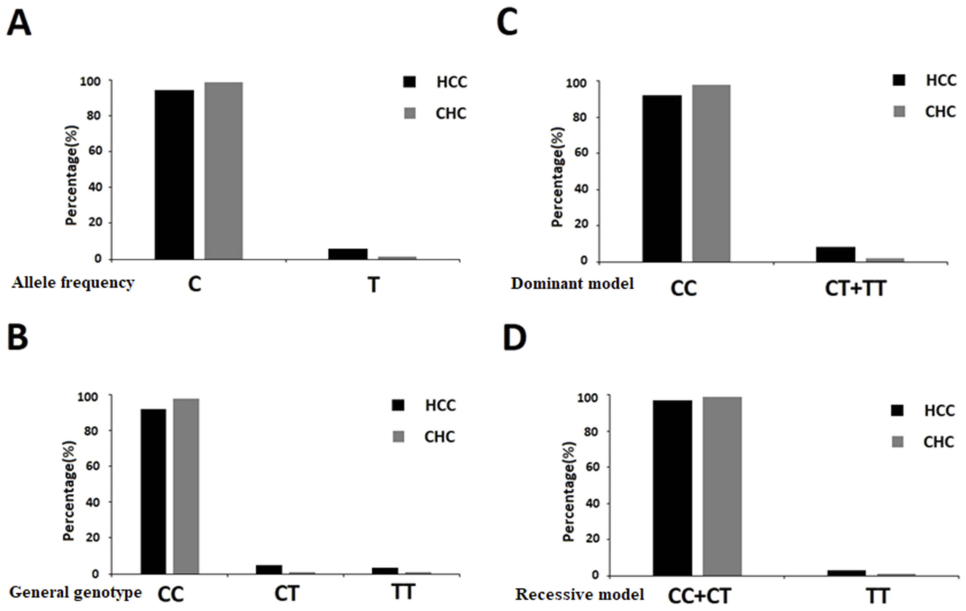

Figure 2 Association between *IFNL3* rs12979860 polymorphism and HCC risk under different genetic models.
Notes: (**A**) Genetic model of allele frequency; (**B**) genetic model of general genotype; (**C**) dominant model; (**D**) recessive model.
Abbreviations: HCC, hepatocellular carcinoma; CHC, chronic hepatitis C; IFNL3, interferon lambda-3.

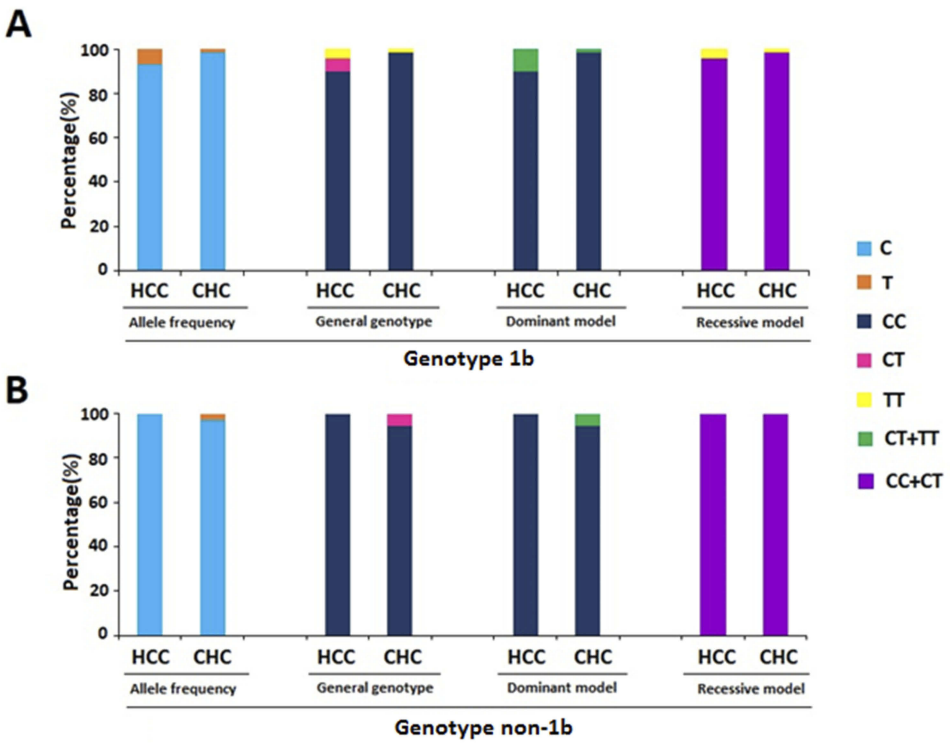

Figure 3 Association between *IFNL3* rs12979860 polymorphism and HCC risk stratified by genotype.
Notes: (**A**) HCV genotype 1b group; (**B**) HCV genotype non-1b group.
Abbreviations: HCC, hepatocellular carcinoma; CHC, chronic hepatitis C; IFNL3, interferon lambda-3; HCV, hepatitis C virus.

IFNL3 polymorphism may affect the efficiency of the immunomodulatory process, which could lead to HCC. The exact molecular mechanisms by which *IFNL3* rs12979860 polymorphism influence susceptibility to HCV-related HCC warrant further elucidation.

There are also some potential limitations in the study, principally limited to a relatively small sample size in a Chinese population at a single center. Further studies involving large-scale samples from different centers should be performed.

Conclusion

In summary, our results indicate that *IFNL3* rs12979860 T allele could be a factor that increases the risk of HCV-related HCC, especially those subjects with CHC genotype 1b infection in the Chinese population. Screening genetic polymorphism of *IFNL3* rs12979860 might be helpful in designing effective and efficient HCC surveillance programs for chronic HCV-infected patients.

Abbreviations

IFNL3, interferon lambda-3; IL28B, interleukin 28B; HCC, hepatocellular carcinoma; SNP, single nucleotide polymorphism; CHC, chronic hepatitis C; HCV, hepatitis C virus; LC, liver cirrhosis; IFN-λ3, IFN lambda-3; SNP, single nucleotide polymorphism; HBV, hepatitis B virus; HIV, human immunodeficiency virus; BMI, body mass index.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Ethics approval and consent to participate

Written informed consent was obtained from all participants included in the present study. Ethical approval to carry out the study was obtained from the Ethics Committee of Tianjin Second People's Hospital. This study was conducted in accordance with the Declaration of Helsinki.

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Author contributions

WH and WKS conceived and designed the study. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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