Hepat Mon. 2017 September; 17(9):e11706. doi: 10.5812/hepatmon.11706.

Published online 2017 September 19. **Research Article**

Interleukin 28B Genetic Polymorphism and Spontaneous Recovery from Hepatitis B Virus Infection in an Iranian Azeri Population

Jafar Mehdizadeh Baghbani,[1] Sousan Mirnajd Gerami,[2] Morteza Ghojazadeh,[3] Morteza Jabbarpour Bonyadi,[4] and Mohammad Hossein Somi[1,*]

[1]MD, Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]MSc, Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]MD, Iranian Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[4]PhD, Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[*]*Corresponding author*: Mohammad Hossein Somi, Liver and Gastrointestinal Diseases Research Center, Imam Reza Hospital, Golgasht Ave, Tabriz, East Azerbaijan, Iran. Tel/Fax: +98-4133367479, E-mail: mhosseinsina@yahoo.com

Received 2016 October 26; **Revised** 2017 June 26; **Accepted** 2017 September 03.

Abstract

Background: Detection of single-nucleotide polymorphisms (SNPs) near the Interleukin 28B (IL28B) gene, which significantly effects the outcome of chronic hepatitis C virus has a substantial impact on research in the field of personalize medicine. In this study, the researchers investigated the influence of *IL28B* polymorphisms on spontaneous recovery from hepatitis B (HBV) infection in an Iranian sample.

Methods: In this case-control study, 177 patients with chronic HBV infection (n = 83, HBsAg (+) for > 6 months, anti-HBc (+), and anti-HBs (-)) or spontaneous recovery (n = 94; HBsAg (-), anti-HBc (+), and anti-HBs (+)) were evaluated. All cases were Iranian with an Azeri ethnic background. The SNPs at rs12979860 and *rs8099917 near IL28B* coding region were assessed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: Regardless of the condition for HBV infection, *rs8099917* TT was most frequently identified (65.0%) followed by *rs12979860* CT (52.5%). All other genotypes were detected as well as all types of haplotype combinations, except for *rs8099917* GT- *rs12979860* CC, which was not identified in any participant. The prevalence of TT *rs8099917* was significantly higher in the chronic HBV group than in the spontaneously recovered individuals (P = 0.038, OR = 1.435). Differences were not significant for *rs12979860*. Using combination of genotypes did not show better odds ratio (P > 0.05).

Conclusions: The SNP upstream of *IL28B* might have an influence on spontaneous HBV recovery.

Keywords: Hepatitis B, Polymorphism, Single Nucleotide/Genetics, Genotype, Interleukins

1. Background

Clinical medicine is now enjoying opportunities, which are brought by recent major progress in basic sciences. These advances might lead to improvement of health care by adapting a unique medical intervention at the right time for the right person. This approach, known as "personalized medicine", is achievable through different levels, beginning from predicting the risk among healthy individuals to predicting the therapeutic response. Genomic information could provide a crucial base for guiding personalized medicine.

One of the best examples for this, though still remains controversial, is the result of genome-wide association studies showing that genetic polymorphisms near the interleukin 28B gene (*IL28B*; including *rs12979860*, *rs12980275*, and *rs8099917*) in patients with chronic hepatitis C, are associated with higher rates of sustained virological response to peginterferon alpha and ribavirin (1-5). Moreover, a relationship has also been reported between *IL28B* polymorphism and spontaneous clearance of HCV infection (1, 6, 7). The interferon, which is coded by *IL28B* (i.e. IFN-λ) is known to play a role in defense against several viral infections, including hepatitis C and Hepatitis B Virus (HBV) (8). Therefore, the effect of *IL28B* polymorphism might not be specific to the immune response against infection with hepatitis C virus.

Results of studies evaluating the association between polymorphism of *ILB28* and natural course of HBV or the response to treatment are divergent. Following negative results for a role for *IL28B* polymorphisms in spontaneous recovery of HBV (9, 10), large cohorts of patients with Chronic Hepatitis B (CHB) demonstrated that *IL28B* polymorphisms were independently related to serological responses to treatment with PEG-IFN (11, 12).

However, negative results on the spontaneous clearance of HBV were replicated (13) and studies indicated that the Single-Nucleotide Polymorphism (SNP) that

has the strongest genetic association with HCV recovery (*rs12979860*) had no association with spontaneous recovery from HBV infection. Moreover, another study indicated an inverse influence of this SNP on HBV recovery (14). Thus, this polymorphism might have had a dissimilar effect on treatment outcome and spontaneous clearance of HBV infection. However, these results are not yet conclusive.

Despite the decline in HBV infection prevalence, the increasing overall number of chronic HBV infection is still a major health problem worldwide, including Iran (15-18). The situation calls for research in different populations to find the targeted treatment approaches. In the current study, the researchers investigated the influence of the *IL28B* polymorphism on HBV infection in a sample from the Iranian population.

2. Methods

2.1. Patients

The sample for this case-control study included Iranian Azeri patients with chronic hepatitis B virus infection (CHB) and those who Spontaneously Recovered (SR) from HBV infection. The protocol was confirmed by the regional ethnics committee, Tabriz University of Medical Sciences. All of participants provided written informed consent for participation and use of their genetic material for this study.

Between June 2015 and June 2016, patients with CHB infection, who visited the associated University clinic were recruited as the CHB group (HBsAg (+) for > 6 months, anti-HBc (+), and anti-HBs(-)). The SR subjects were selected from family members of HBV infected patients or those registered with the AZAR Cohort study (method described elsewhere) and were HBsAg (-), anti-HBc (+), and anti-HBs (+). A patient educational session was provided for all of participants.

All subjects were native Azeri Iranians. The exclusion criteria were as follows, (1) vaccinated subjects, who were positive for anti-HBs alone, but negative for anti-HBc, (3) co-infection with hepatitis C or human immunodeficiency viruses, and (4) presence of other chronic liver disease, such as primary biliary cirrhosis, autoimmune hepatitis, and decompensated liver disease. The researchers excluded 12 patients with chronic hepatitis B and 10 spontaneously recovered subjects. Fifteen patients from the spontaneously recovered group did not show, thus this study included 83 patients in the CHB group and 94 in the SR group.

2.2. Laboratory Tests

The HBV serological markers for HBsAg, anti-HBc, and anti-HBs were conducted with the Enzyme Linked Immunosorbent Assays (ELISAs).

2.3. Interleukin 28B Genotyping

Genomic DNA was extracted using a Ferments DNA Blood Kit (Ferments, France), according to the manufacturer's instructions from peripheral blood samples. Quality control and subsequent handling of the DNA was carried out in the researchers own laboratory.

The genotyping of SNPs rs12979860 and *rs8099917* was carried out by Polymerase Chain Reaction And Restriction Fragment Length Polymorphism (PCR-RFLP). For rs12979860, the primer sequences were 5'- GCG GAA GGA GCA GTT GCG CT -3' (Rs12-F) and 5'- GGG GCT TTG CTG GGG GAG TG -3' (Rs-12-R). For *rs8099917*, the oligonucleotide primers were 5'- CCC ACT TCT GGA ACA AAT CGT CCC -3' (Rs80-F) and 5'- TCT CCT CCC CAA GTC AGG CAA CC -3' (Rs80-F) (19).

For the RFLP assay, the PCR amplicon containing the rs12979860 SNP was digested with 10 units of Bsh1236I (BstUI) restriction endonuclease and the PCR amplicon containing the *rs8099917* SNP was digested with 10 units of BseMI (BsrDI) restriction endonuclease for at least 1 hour.

The digested PCR products were separated on 3% agarose gel, containing ethidium bromide and a visualized gel documentation system (Figure 1). The *rs12979860* CC genotype produced two 196-bp and 45-bp fragments, the CT genotype produced three 241-, 196-, and 45-bp fragments and the TT genotype produced a 241-bp fragment. The *rs8099917* TT genotype produced a 552-bp fragment, the GT genotype produced three 552-, 322- and 230-bp fragments and the GG genotype produced two 322- and 230-bp fragments.

2.4. Statistical Analysis

Data are expressed as the means (standard deviation) and medians (range) for age, and numbers (%) for genotype. The laboratory findings were compared among the groups using Chi-square tests and SPSS version 17.0 (SPSS, Inc., Chicago, IL). A P value of < 0.05 on a two-tailed test was considered statistically significant.

3. Results

The median age of the subjects in the SR (52 males and 42 females) and the CHB groups (47 males and 36 females) was 38 and 44 years, respectively. The mean and Standard Deviation (SD) was 37.5 ± 10.3 and 39.1 ± 9.8, respectively. Gender distribution was not different between the 2 groups ($P = 0.812$).

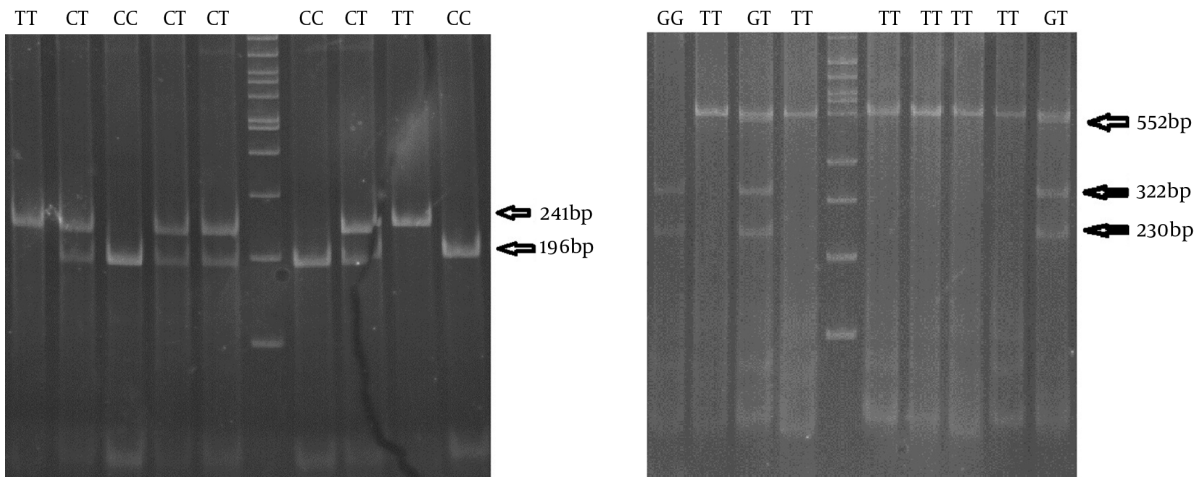

Figure 1. Prevalence of Combination of Genotypes in the Study Sample

3.1. Prevalence of rs12979860 and rs8099917

Regardless of group, *rs12979860* CT was identified in more than 50% of participants (65.0% in the SR, and 52.5% in the CHB group). The *rs8099917* TT was also the most prevalent (56.4% in the SR and 74.7% in the CHB group; 65% total prevalence).

Distribution of *rs12979860* polymorphisms was not different between the 2 groups (P = 0.224). However, the prevalence of TT *rs8099917* was significantly higher in the CHB group than in the SR subjects (P = 0.038, OR = 1.435 (1.1 to 1.872)). Results are shown in Table 1.

Table 1. Prevalence of Different Genotypes in Selected Loci Near the *IL28B* Gene in the Study Sample

Variables	Spontaneous Recovery	Chronic Hepatitis B
rs12979860		
No.	94	83
CC	28 (29.8)	31 (37.3)
CT	49 (52.1)	44 (53.0)
TT	17 (18.1)	8 (9.6)
C allele	105	106
T allele	83	60
rs8099917		
No.	94	83
GG	9 (9.6)	4 (4.8)
GT	32 (34.0)	17(20.7)
TT	53 (56.4)	62 (74.7)
G allele	50	25
T allele	138	141

3.2. Combination of Genotypes

Frequencies for combination of genotypes using *rs12979860* and *rs8099917* are presented in Figure 2. As shown in this all all types of combinations were observed in both groups, except for *rs8099917* GT- *rs12979860* CC. This also also shows that *rs8099917* TT- *rs12979860* CT is the most prevalent in the CHB group and *rs8099917* TT- *rs12979860* CC is the most prevalent in the SR group.

Combination of genotypes did not show statistically better odd ratios (all P > 0.05).

4. Discussion

Results of this study indirectly showed the pattern of *IL28B* upstream polymorphisms in the Iranian population. In several studies from Hong Kong (20), Australia (21), Korea (13, 14), and China (22), *rs12979860CC* was the most common genotype regardless of hepatitis infection status with a noticeable difference to other genotypes. This difference decreased in studies from Arabian countries (23) where *rs12979860CC* was still foremost. On the other hand, *rs12979860CT* is the most common genotype reported by studies from Turkey (24, 25), similar to the current results from Iranian Azeri-Turk population. However, this similarity is not restricted to inhabitants of Azerbaijan province yet are reported from other parts of Iran as well (19, 26). Fewer data are available about polymorphism in *rs8099917*,

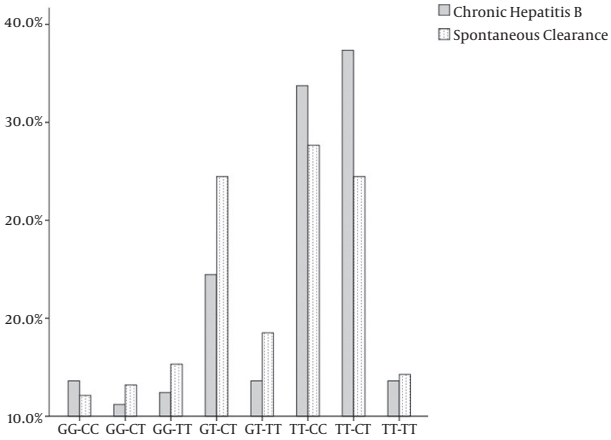

Figure 2. The RFLP Analysis Generated by *IL28B* Specific Primers Targeting *rs12979860* and *rs8099917*

and comparable to the current results; *rs8099917TT* is the most common (13, 14, 20). Though this dominance is more obvious in some report, *rs8099917GG* was not detected in a Korean sample (27).

In the current study, the researchers genotyped *IL28B* polymorphisms (*rs8099917* and *rs12979860*) in Iranian Azeri patients with chronic hepatitis B and those who spontaneously recovered from HBV infection, to determine its possible influence on HBV infection outcome in a natural history setting. The current results are in line with previous studies indicating a different role for *IL28B* polymorphisms in the natural course of HBV infection compared to HCV.

In contrast to a previous study (9), *IL28B* polymorphisms (*rs8099917*) was significantly associated with the outcome of HBV infection in the current sample. This result has previously been reported by other studies as well (14). Conversely, the prevalence of the favorable predictor in terms of spontaneous recovery from HCV infection (i.e. *rs12979860CC*) was not related to natural course of HBV in the current sample. This finding has also been reported in several previous studies from other populations (28).

Product of *IL28B* gene, is a cytokine that ultimately upregulates the IFN-stimulated genes (29, 30). Though the mechanism is not clear, this cytokine plays a critical role in the immune response to HCV infection and increasing evidences show its effect on outcome of both natural and IFN-α-treated HCV infections (1, 31). However, there is still controversy on the topic of the association between *IL28B* genetic polymorphism and both natural and treated HBV infection (32).

Following the first positive report about the association between *IL28B* polymorphism and chronic HBV infection (12), which proposed that *rs12980275AA* is independently associated with HBeAg seroconversion after PEG-IFN treatment in CHB, there have been several negative results.

One study concluded that the *rs12979860CC* genotype, which has the strongest genetic association with HCV recovery, was not associated with spontaneous recovery of HBV infection (9). Another study reported a significant but reverse association compared to HCV results and showed higher prevalence of *rs12979860CC* and *rs8099917TT* in patients with CHB compared to spontaneously recovered subjects (14). This is why in patients with HCV infection, *rs12979860CC* is associated with a 2- to 3-fold higher response to treatment (1) and spontaneous clearance (6), and there are evidences that presence of *rs8099917TT* might increase this association (33). As a result, the mechanism of immune response in which product of this gene takes a part, might be different for HBV and HCV infections. This may be a result of differences between HBV and HCV infection (34), characteristics of *IL28B* (35) or a combination of both. However, this hypothesis and the current results should be replicated in future studies. The present result could also be included in prospective studies so that together with other biomarkers that might effect the course of illness (36), they could end with a precised method of intervention for each patient.

In conclusion, the SNP upstream of *IL28B* has an important role in natural course of HBV infection that might be different from HCV infection.

Footnotes

Authors' Contribution: Mohammad Hossein Somi developed the original idea and the protocol, supervised the study and gave administrative support. Morteza Jabbarpour Bonyadi and Susan Mirnajd Gherami contributed to development of the protocol and data acquisition. Morteza Ghojazadeh abstracted and analyzed the data. Jafar Mehdizadeh Baghbani contributed to data acquisition and wrote the manuscript.

Financial Disclosure: The authors had no financial interests related to the material in this manuscript.

Role of the Sponsor: The LGDRC is an academic institution and had no role in the design and conduct of the study, collection, management, and analysis of the data. The LGDRC provided logistic arrangements for interview sessions with patients.

Funding/Support: This study was supported by the Liver and gastrointestinal diseases research center (LGDRC), Tabriz University of Medical Sciences.

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