Role of IL-28B genetic variants in HCV-related liver disease severity in patients with different viral genotypes

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Abstract

Reports of the role of host interleukin 28B (IL-28B) genetic variants in liver disease severity in patients with chronic hepatitis C (CHC) have obtained conflicting results. The impact of IL-28B in Asian patients with different viral genotypes remains elusive.

We try to elucidate the effect of IL-28B genetic variants in a large Asian cohort with different viral genotypes.

The association between the IL-28B rs8099917 genotype and liver fibrosis was investigated in 1288 patients with biopsy-proven CHC.

Patients with hepatitis C virus genotype 1 (HCV-1) infection comprised 59.4% of the population. The remaining 40.6% (518 patients) did not have HCV-1 infection. Of the 1084 patients with the IL-28 genotype, 85.6% (928 patients) had the TT genotype. Univariate analysis revealed that, compared to patients without advanced liver fibrosis, patients with advanced liver fibrosis (Metavir fibrosis score 3–4) had an older age, a lower platelet count, a higher α-fetoprotein level, a higher alanine aminotransferase level, a higher incidence of diabetes, and a higher frequency of rs8099917 non-TT genotype carriage.

Logistic regression analysis revealed that factors significantly associated with advanced liver fibrosis included age (odds ratio [OR] 95% confidence interval [CI]: 1.023/1.009–1.037, P = .001), diabetes (OR/CI: 1.736/1.187–2.539, P = .004), α-fetoprotein (OR/CI: 1.007/1.002–1.012, P = .009), platelet count (OR/CI: 0.991/0.988–0.993, P < .001), and carriage of the rs8099917 non-TT genotype (OR/CI: 0.585/0.400–0.856, P = .006). When patients were classified by viral genotype, factors that had significant independent associations with advanced liver fibrosis in patients with HCV-1 infection included diabetes (OR/CI: 2.379/1.452–3.896, P = .001), α-fetoprotein (OR/CI: 1.023/1.012–1.035, P < .001), platelet count (OR/CI: 0.99/0.987–0.994, P < .001), and carriage of the rs8099917 non-TT genotype (OR/CI: 0.529/0.328–0.854, P = .009). In patients who had advanced liver fibrosis but not HCV-1 infection, factors that had significant independent associations with advanced liver fibrosis included age (OR/CI: 1.039/1.016–1.063, P = .001) and platelet count (OR/CI: 0.99/0.986–0.995, P < .001); additionally, IL-28B genetic variants were not associated with liver disease severity.

Unfavorable IL-28B genetic variants were associated with advanced liver disease. The genetic effect is limited to patients with HCV-1 infection.

Abbreviations: ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, CHC = chronic hepatitis C, CI = confidence interval, FIB-4 = fibrosis index based on 4 factors, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IL-28B = interleukin 28B, OR = odds ratio, SNP = single-nucleotide polymorphism.

Keywords: CHC, IL-28B, liver fibrosis, SNP

Received: 4 May 2017 / Received in final form: 4 December 2017 / Accepted: 10 January 2018
http://dx.doi.org/10.1097/MD.0000000000009782

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1. Introduction
An estimated 130 to 170 million people worldwide are currently infected with hepatitis C virus (HCV), and more than 350,000 people die from chronic hepatitis C (CHC)-related end-stage liver disease each year.[11] Notably, 50% to 80% of patients acutely infected with HCV eventually have chronic hepatitis.[2] Notably, 10% to 20% of patients with HCV infection are diagnosed with liver cirrhosis within 20 to 30 years. In patients with liver cirrhosis, the annual incidence of hepatocellular carcinoma (HCC) is 1% to 8%. Factors associated with CHC-related liver fibrosis progression and clinical outcome include age, time because initial HCV infection,[11] hepatitis B virus or human immunodeficiency virus (HIV) coinfection, obesity, hepatic steatosis, alcoholism,[4,5] and nonresponse to antiviral therapy.[6,7] The host genetic predispositions are considered another important determinant of progression and outcome in liver fibrosis.[8–11]

Studies based on genome-wide associated studies have shown that single-nucleotide polymorphisms (SNPs) at or near the interleukin 28B (IL-28B) gene play a role in the management of HCV infection. Emerging evidence indicates that favorable genetic variants of IL-28B may increase the efficacy of interferon-based treatment for HCV genotype-1 (HCV-1).[16–20]

However, the literature is inconsistent regarding the impact of what on liver disease severity in CHC patients.[14,21–26] The discordant results may be attributable to diverse study designs and patient characteristics. Notably, most studies of what have been performed in the West, where the prevalence of HCV-1 infection is high. Although viral genotypes reportedly differ in their distribution of IL-28B genotypes,[27] few studies have investigated associations between IL-28B genetic variants and liver disease severity in patients with different viral genotypes. Therefore, the current study investigated this association in a large cohort of Asian patients who had biopsy-proven infection with HCV-1 or HCV-2.

2. Methods
2.1. Patients
This study analyzed 1288 CHC patients recruited from 1 medical center and 2 regional core hospitals from 2001 to 2011. All patients had been referred for pegylated interferon/ribavirin antiviral therapy, and liver biopsy was performed before treatment. The exclusion criteria were coinfection with HIV, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson disease, α1-antitrypsin deficiency, and any history of the following: alcohol abuse (≥20 g daily), psychiatric condition, liver transplantation, or HCC. Anti-HCV antibodies were detected using a commercially available third-generation enzyme-linked immunosorbent assay kit (AxSYM 3.0, Abbott Laboratories, Chicago, IL.). Serum HCV RNA was detected using real-time polymerase chain reaction (COBAS AMPLICOR Hepatitis C Virus Test, ver. 2.0; Roche, Branchburg, NJ). The detection limit: 50 IU/mL). The HCV genotypes were determined using the Okamoto method.[28] The biochemical parameters were measured with a multichannel auto analyzer (Hitachi Inc, Tokyo, Japan). The liver histology was graded and staged according to the scoring system described by Scheuer.[29] To overcome the sampling variability in liver biopsies, associations with genetic variants were evaluated in patients with bridging fibrosis (F3–F4) and not in patients who only had cirrhosis.[11,30] The study was approved by the ethics committees at the participating hospitals and was performed according to the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients gave written informed consent before enrollment.

2.2. IL-28B genotyping and statistical analyses
As in previous works, rs8099917 was selected as the candidate SNP.[31,32] The genotypes of the patients were determined using methods described previously.[33] Frequency was compared between groups by chi-squared test with Yates correction or by Fisher exact test. Group means, presented as mean values standard deviation, were compared using analysis of variance and the Student t test or the Mann–Whitney U test. The serum HCV RNA levels were expressed after logarithmic transformation of original values. Severity of liver fibrosis was indicated by the aspartate aminotransferase (AST):to-platelet ratio index (APRI) calculated by the following equation: (AST level/upper limit of normal range)/platelet counts (10^9/L) × 100.[34] Fibrosis index based on 4 factors (FIB-4) was calculated as age [year] × AST [ULN]/[PLT [10^9/L] × (ALT [ULN])/(1/2)].[35] The frequencies of the rare allele (G) of rs8099917 genotype were too low, and the rare homozygote (GG) and heterozygote (GT) were combined in analyses of SNPs. A stepwise logistic regression analysis was performed to evaluate the independent factors associated with advanced liver fibrosis by analyzing the covariants with P values <.05 in the univariate analysis. The area under the curve was compared using receiver operating characteristic analysis to determine the cut-offs for using APRI and FIB-4 level to predict advanced liver fibrosis. The statistical analyses were performed using the SPSS 12.0 statistical package (SPSS, Chicago, IL). All statistical analyses were based on 2-sided hypothesis tests with a significance level of P < .05.

3. Results
3.1. Patient profiles
Table 1 shows the basic demographic, virological and clinical features of the 1288 patients. The mean age was 52.2 ± 11.7 years, and males comprised 56.0% of the population. The mean HCV RNA levels were 5.4 ± 1.0 log IU/mL. Patients with

| Table 1 | Baseline characteristics and clinical features of the patients. |
|---|---|
| All patients (N = 1288) | |
| Age, y (mean ± SD) | 52.2 ± 11.7 |
| Male gender, n (%) | 721 (56.0) |
| Body weight, kg (mean ± SD) | 65.3 ± 11.2 |
| Diabetes, n/N (%) | 175/1286 (13.6) |
| Platelet count, × 10^9 μL (mean ± SD) | 164.1 ± 61.0 |
| AST, IU/L (mean ± SD) | 103.2 ± 61.4 |
| ALT, IU/L (mean ± SD) | 152.6 ± 97.1 |
| α-Fetoprotein, ng/mL (mean ± SD) | 17.3 ± 49.0 |
| HCV genotype 1, n/N (%) | 759/1277 (59.4) |
| HCV viral loads, log IU/mL (mean ± SD) | 5.4 ± 1.0 |
| HBsAg (+), n/N (%) | 107/1286 (8.3) |
| IL-28B rs8099917 genotype | |
| HCV, n/N (%) | 928/1286 (72.4) |
| FIB-4 | 3.4 ± 2.9 |

ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, FIB-4 = fibrosis index based on 4 factors, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, IL-28B = interleukin 28B, SD = standard deviation.
advanced fibrosis (F3–F4) comprised 32.6% of the population. Patients with HCV-1 infection comprised 59.4%. The remaining 40.6% (518 patients) had HCV-2 (39.4%), HCV-3 (0.1%), or an unclassified HCV genotype (1.1%). Of the 1084 patients with IL-28 genotype, 928 (85.6%) patients had the rs8099917 TT genotype.

### 3.2. Factors associated with advanced liver fibrosis

Univariate analysis revealed that patients with advanced liver fibrosis were characterized by advanced age, low platelet count, high α-fetoprotein, high AST level, a high proportion of diabetes, and carriage of the rs8099917 non-TT genotype. Factors that significantly associated with advanced liver fibrosis included age (odds ratio [OR]/95% confidence interval [CI]: 1.023/1.009–1.037, \( P = .001 \)), diabetes (OR/CI: 1.736/1.187–2.539, \( P = .004 \)), α-fetoprotein (OR/CI: 1.007/1.002–1.012, \( P = .009 \)), platelet count (OR/CI: 0.991/0.988–0.993, \( P < .001 \)), and carriage of the rs8099917 non-TT genotype (OR/CI: 0.585/0.400–0.856, \( P = .006 \)). Table 3 shows that the APRI or/and FIB-4 did not change the effect of IL-28 SNP on liver fibrosis.

### 3.3. Factors associated with liver fibrosis stratified by viral genotype

The effect of IL-28B SNP on liver fibrosis was further explored in patients with different viral genotypes (Table 4). The HCV-1 patients with advanced liver fibrosis were characterized by advanced age, low platelet count, high α-fetoprotein, high AST level, high incidence of diabetes, and carriage of the rs8099917 non-TT genotype. Factors that had significant independent associations with advanced liver fibrosis included age (odds ratio [OR]/95% confidence interval [CI]: 1.023/1.009–1.037, \( P = .001 \)), diabetes (OR/CI: 1.736/1.187–2.539, \( P = .004 \)), α-fetoprotein (OR/CI: 1.007/1.002–1.012, \( P = .009 \)), platelet count (OR/CI: 0.991/0.988–0.993, \( P < .001 \)), and carriage of the rs8099917 non-TT genotype (OR/CI: 0.585/0.400–0.856, \( P = .006 \)).

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### Table 2

Univariate analysis of factors associated with advanced liver fibrosis.

| Variables                          | All patients (\( N = 1288 \)) | F0–F2 (\( n = 868 \)) | F3–F4 (\( n = 420 \)) | \( P \) |
|-----------------------------------|-------------------------------|---------------------|----------------------|-----|
| Age, y (mean ± SD)                | 52.2 ± 11.7                   | 50.4 ± 11.8         | 56.1 ± 10.4          | <.001 |
| Male gender, n (%)                | 721 (60.0)                    | 498 (57.4)          | 223 (63.1)           | .15  |
| Body weight, kg (mean ± SD)       | 65.3 ± 11.2                   | 64.9 ± 11.2         | 66.1 ± 11.3          | .08  |
| Diabetes, n (%)                   | 175/1286 (13.6)               | 93/868 (10.7)       | 82/418 (19.6)        | <.001 |
| Platelet count, × 10^3 μL (mean ± SD) | 164.1 ± 61.0                | 177.2 ± 55.6        | 139.9 ± 63.6         | <.001 |
| AST, IU/L (mean ± SD)             | 103.2 ± 61.4                  | 97.3 ± 60.3         | 115.5 ± 61.9         | <.001 |
| ALT, IU/L (mean ± SD)             | 152.6 ± 97.1                  | 152.6 ± 97.9        | 152.6 ± 97.9         | .99  |
| α-Fetoprotein, ng/mL (mean ± SD)  | 17.3 ± 40.0                   | 11.5 ± 30.5         | 29.4 ± 72.4          | <.001 |
| HCV genotype 1, n (%)             | 759/1277 (60.8)               | 510/863 (59.1)      | 249/414 (60.1)       | .72  |
| HCV viral loads, log IU/mL (mean ± SD) | 5.4 ± 1.0                    | 5.4 ± 1.0           | 5.3 ± 1.0            | .31  |
| HBsAg (+), n/N (%)                | 107/1286 (8.3)                | 80/868 (9.2)        | 27/418 (6.5)         | .09  |
| IL-28B rs8099917 genotype         | 928/1084 (85.6)               | 657/746 (82.1)      | 271/338 (80.2)       | .001 |
| APRI                              | 1.9 ± 1.6                     | 1.6 ± 1.3           | 2.6 ± 2.0            | <.001 |
| FIB-4                             | 3.4 ± 2.9                     | 2.7 ± 2.0           | 4.9 ± 3.7            | <.001 |

ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, FIB-4 = fibrosis index based on 4 factors, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, IL-28B = interleukin 28B, SD = standard deviation.

### Table 3

Logistic regression analysis of factors associated with advanced liver fibrosis.

| Variables                          | Model 1: without APRI and FIB-4 | Model 2: with APRI | Model 3: with APRI and FIB-4 |
|-----------------------------------|---------------------------------|-------------------|-----------------------------|
|                                    | OR                              | 95% CI            | \( P \) | OR | 95% CI | \( P \) | OR | 95% CI | \( P \) |
| Age, per 1 y increase              | 1.023                           | 1.009–1.037       | .001 | 1.024 | 1.010–1.038 | .001 | 1.012 | 1.001–1.013 | <.001 |
| Diabetes                           |                                 |                   |     | 1.005 | 1.000–1.010 | .06  | 1.005 | 1.000–1.010 | .03  |
| Platelet count, × 10^3 μL          |                                 |                   |     | 0.990 | 0.986–0.994 | <.001 | 0.996 | 0.993–0.999 | .01  |
| α-Fetoprotein, per 1 mg/mL increase |                                 |                   |     | 1.007 | 1.002–1.012 | .09  | 1.005 | 1.000–1.010 | <.001 |
| AST, per 1 IU/L increase           |                                 |                   |     | 1.005 | 1.000–1.010 | .06  | 1.005 | 1.000–1.010 | .03  |
| IL-28B rs8099917 genotype          |                                 |                   |     | 0.999 | 0.992–0.999 | <.001 | 0.999 | 0.993–0.999 | .01  |
| Non-TT                             |                                 |                   |     | 0.585 | 0.400–0.856 | <.001 | 0.628 | 0.427–0.925 | .02  |
| APRI                               |                                 |                   |     | 1.509 | 1.295–1.509 | <.001 | 1.509 | 1.295–1.509 | <.001 |
| FIB-4                              |                                 |                   |     | 1.509 | 1.295–1.509 | <.001 | 1.509 | 1.295–1.509 | <.001 |

APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, CI = confidence interval, FIB-4 = fibrosis index based on 4 factors, IL-28B = interleukin 28B, OR = odds ratio, TT = rs8099917 TT genotype.
Factors independently associated with advanced liver fibrosis in patients with HCV-non-1 infection included age (OR/CI: 1.039/1.016–1.063, \( P = .001 \)) and platelet count (OR/CI: 0.990/0.986–0.995, \( P < .001 \)). The IL-28B genotype was not a determinant of liver fibrosis. The results remained consistent when APRI and/or FIB-4 were considered (Table 5).

Next, the effects of APRI and FIB-4 on pathology fibrosis grade were considered. Both APRI and FIB-4 correlated positively with advanced liver fibrosis in both univariate and logistic regression analyses. Compared with APRI, however, FIB-4 had a stronger

### Table 4
Univariate analysis of factors associated with advanced liver fibrosis stratified by HCV genotype.

| Variable                        | HCV genotype 1 | HCV genotype non-1 |
|--------------------------------|----------------|--------------------|
|                               | F0–F2 (n = 510) | F3–F4 (n = 249)    | P      | F0–F2 (n = 353) | F3–F4 (n = 165) | P      |
| Age, y (mean ± SD)             | 49.6 ± 11.9    | 55.1 ± 11.1        | .001   | 51.7 ± 11.5    | 57.4 ± 9.2     | .001   |
| Male gender, n (%)             | 315 (61.8)     | 137 (55.0)         | .08    | 180 (51.1)     | 82 (49.7)      | .78    |
| Body weight, kg (mean ± SD)    | 65.2 ± 11.3    | 66.1 ± 10.7        | .27    | 65.4 ± 11.1    | 66.1 ± 12.3    | .13    |
| Diabetes, n (%)                | 53/510 (10.4)  | 51/248 (20.6)      | .001   | 38/353 (10.8)  | 29/165 (17.6)  | .03    |
| Platelet count, \( \times 10^3 \) μL (mean ± SD) | 179.5 ± 55.5 | 139.8 ± 64.4      | .001   | 173.5 ± 56.0     | 140.3 ± 62.9 | .001   |
| ALT, IU/L (mean ± SD)          | 49.4 ± 60.9    | 114.1 ± 58.5       | < .001 | 101.9 ± 59.6    | 118.2 ± 66.9   | .008   |
| AST, IU/L (mean ± SD)          | 146.6 ± 97.8   | 150.6 ± 90.4       | .56    | 162.9 ± 97.9    | 155.8 ± 103.2 | .52    |
| α-Fetoprotein, ng/mL (mean ± SD) | 10.4 ± 24.7   | 32.7 ± 79.8        | < .001 | 15.2 ± 57.6     | 24.7 ± 60.2    | .03    |
| HCV viral loads, log IU/mL (mean ± SD) | 5.6 ± 1.0     | 5.6 ± 0.9          | .69    | 5.1 ± 1.0       | 5.0 ± 1.0      | .25    |
| HBsAg (+), n (%)               | 56/510 (11.0)  | 13/248 (5.2)       | .01    | 24/353 (6.8)    | 12/165 (7.3)   | .84    |
| IL-28B ns8099917 genotype TT, n (%) | 398/455 (87.5) | 150/199 (75.4) | < .001 | 254/286 (88.8)  | 120/137 (87.6) | .71    |
| APRI                           | 1.5 ± 1.2      | 2.5 ± 1.9          | < .001 | 1.7 ± 1.4       | 2.7 ± 2.1      | < .001 |
| FIB-4                          | 2.6 ± 1.8      | 4.8 ± 3.7          | < .001 | 2.9 ± 2.3       | 5.1 ± 3.7      | < .001 |

ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, FIB-4 = fibrosis index based on 4 factors, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, IL-28B = interleukin 28B, SD = standard deviation, TT = rs8099917 TT genotype.

### Table 5
Logistic regression analysis of factors associated with advanced liver fibrosis in patients with different HCV genotypes.

| Variables                | Model 1: without APRI and FIB-4 as covariates | Model 2: with APRI as covariate | Model 3: with APRI and FIB-4 as covariates |
|--------------------------|----------------------------------------------|--------------------------------|------------------------------------------|
|                          | OR 95% CI P                                | OR 95% CI P                    | OR 95% CI P                              |
| HCV genotype 1           |                                              |                                |                                          |
| Diabetes                 |                                             |                                |                                          |
| No                       | 1                                            | 1                              | 1                                         |
| Yes                      | 2.379 (1.452–3.896)                         | 2.280 (1.378–3.771)            | 2.381 (1.443–3.929)                      |
| Platelet count           |                                              |                                |                                          |
| Per 10^3 μL increase     | 0.990 (0.987–0.994)                         | .001                           |                                          |
| α-Fetoprotein            |                                              |                                |                                          |
| Per 1 ng/mL increase     | 1.023 (1.012–1.035)                         | < .001                         |                                          |
| AST                      |                                              |                                |                                          |
| Per 1 IU/L increase      | 0.989 (0.983–0.995)                         | < .001                         |                                          |
| IL-28B rs8099917 genotype |                                             |                                |                                          |
| Non-TT                   | 0.529 (0.328–0.854)                         | .009                           |                                          |
| TT                       | 0.549 (0.341–0.888)                         | .014                           | 0.566 (0.349–0.919)                      | .02 |
| APRI                     | 2.081 (1.604–2.699)                         | < .001                         |                                          |
| FIB-4                    | 1.391 (1.250–1.548)                         | < .001                         |                                          |
| HCV genotype non-1       |                                              |                                |                                          |
| Age                      | 1.039 (1.016–1.063)                         | .001                           | 1.041 (1.017–1.065)                      | .001 |
| Platelet count           |                                              |                                |                                          |
| Per 10^3 μL increase     | 0.987 (0.985–0.990)                         | .001                           |                                          |
| AST                      |                                              |                                |                                          |
| Per 1 IU/L increase      | 0.987 (0.983–0.989)                         | .004                           |                                          |
| APRI                     | 1.009 (1.444–2.523)                         | < .001                         |                                          |
| FIB-4                    | 1.328 (1.217–1.448)                         | < .001                         |                                          |

APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, CI = confidence interval, FIB-4 = fibrosis index based on 4 factors, HCV = hepatitis C virus, IL-28B = interleukin 28B, OR = odds ratio, TT = rs8099917 TT genotype.
association with advanced liver fibrosis in HCV-infected patients. When HCV patients were grouped by presence or absence of HCV genotype 1, both groups showed that liver disease severity had a stronger association with FIB-4 compared with APRI.

4. Discussion
This study showed that host IL-28B genetic variants were associated with liver disease severity in Asian patients. Carriage of the unfavorable genotype IL-28B was independently associated with advanced liver disease in Taiwan patients with CHC. Notably, the impacts of host genomes on liver fibrosis differed by viral genotype. In addition, IL-28B SNP only affected liver disease severity in patients with HCV-1 infection.

The determinants of liver fibrosis progression in CHC are multifactorial, and host genetic variants play a critical role. Studies of genome-wide associations and studies of candidate genes have investigated whether host genetic variants are associated with HCV-related liver fibrosis. For instance, Estrabaud et al reported that patients with cirrhosis have higher than normal frequencies of the Mmp1 2G homozygote at position-1607 and the MMP9 3C allele at position-1562 and that patients with mild fibrosis have a higher than normal frequency of the AA homozygote at position-2518. In CHC patients, carriage of the PNPLA3 rs738409 mutant GG genotype is associated not only with hepatic steatosis, but also with liver fibrosis. All vitamin D receptor gene haplotypes (rs1544410 C, rs7975232 A and rs731236 A, RNP7 rs16581720, and MERTK rs4374383) are reportedly associated with fibrosis progression and cirrhosis development. As expected, IL28B genotypes were significantly associated with advanced liver disease in Taiwan patients with CHC. However, the genetic effect is limited to patients with HCV-1 infection.

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