World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i42.7399

*World J Gastroenterol* 2013 November 14; 19(42): 7399-7404
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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BRIEF ARTICLE

# Interleukin 28B-related polymorphisms: A pathway for understanding hepatitis C virus infection?

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Supported by Grants from the Research Fund from University of Region of Joinville, FAP-UNIVILLE
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Received: January 21, 2013 Revised: August 19, 2013
Accepted: September 4, 2013
Published online: November 14, 2013

## Abstract

**AIM:** To analyze the role of *rs12979860* and *rs8099917* polymorphisms in hepatitis C virus (HCV) genotype 1 infection of Brazilians.

**METHODS:** A total of 145 adult patients diagnosed with genotype 1 chronic hepatitis C (CHC) who had completed a 48-wk regimen of pegylated-interferon α-2a or -2b plus ribavirin combination therapy were recruited from six large urban healthcare centers and 199 healthy blood donors (controls) from a single site between January 2010 and January 2012. Data on the patients' response to treatment was collected. Polymerase chain reaction-restriction fragment length polymorphism genotyping of the interleukin (*IL*)*28B* gene fragment encompassing the single nucleotide polymorphisms (SNPs) rs12979860 (C/T) and rs8099917 (T/G) was carried out for 79 of the CHC patients and 199 of the controls. Bi-directional amplicon sequencing of the two SNPs was carried out for the remaining 66 CHC patients.

**RESULTS:** SNP rs12979860 genotyping was successful in 99.5% of the controls and 97.2% of the CHC patients, whereas the SNP rs8099917 genotyping was successful in 95.5% of the controls and 100% of the

CHC patients. The genotype and allele distributions for both rs12979860 and rs8099917 were significantly different between the control and CHC patient groups, with significantly higher genotype frequencies of CC and TT in the controls ($P$ = 0.037 and 0.046, respectively) and of TT and GG in the CHC patients ($P$ = 0.0009 and 0.0001, respectively). Analysis of the CHC patients who achieved sustained virological response (SVR) to treatment ($n$ = 55) indicated that the rs12979860 C allele and CC genotype were predictors of SVR ($P$ = 0.02). No significant correlation was found between rs8099917 genotypes and treatment response, but carriers of the T allele showed significantly higher rates of SVR ($P$ = 0.02). Linkage disequilibrium analysis of the group that achieved SVR showed a significant association between rs12979860 and rs8099917 ($P$ = 0.07).

**CONCLUSION:** The higher allele frequency of rs12979860 C and rs8099917 T observed in non-HCV-infected individuals may indicate a potential protective role for these *IL28B*-related polymorphisms.

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**Key words:** Hepatitis C; Interleukin 28B; Single nucleotide polymorphisms; Sustained virological response; Brazil

**Core tip:** This study investigated the differential distribution of interleukin 28B genetic variants between patients with chronic hepatitis C genotype 1 infection and non-infected healthy controls, and evaluated the association of these polymorphisms with patient response to standard antiviral therapeutic regimens. Genotype and allele frequencies of rs12979860 and rs8099917 were significantly different between the patients and controls, and the patterns suggested a potential protective role against hepatitis C virus infection. Finally, the rs12979860 CC genotype showed correlation to achievement of sustained virological response following pegylated-interferon/ribavirin-based therapy.

Garcia RFL, Moreira S, Ramos ALA, Ferreira LE, Mattos AA, Tovo CV, Nader LA, Ramos JA, Rondinelli E, Dominici AJ, Garcia CE, Pinho MSL, Brandão-Mello CE, Villela-Nogueira CA, França PHC. Interleukin 28B-related polymorphisms: A pathway for understanding hepatitis C virus infection? *World J Gastroenterol* 2013; 19(42): 7399-7404 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i42/7399.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i42.7399

## INTRODUCTION

Hepatitis C virus (HCV) infection results in a broad spectrum of clinical outcomes and symptoms, ranging from spontaneous viral elimination to chronic infection and from jaundice to end-stage liver failure. Despite the introduction of highly efficacious antiviral drugs based on viral protease inhibition, most countries continue to rely on the established combination therapy based on an immune-modulator plus an antiviral [most frequently pegylated-interferon α-2a or -2b (PegIFN-α-2a/2b) and ribavirin (RBV)] even though this strategy is associated with high failure rates[1]. Studies to uncover the mechanisms underlying non-/low- or unsustained response to treatment have identified a number of contributing factors, related to both the virus itself (*i.e.*, genotype and viral load) and the host (*i.e.*, age, sex, ethnicity, concomitant liver fibrosis, and metabolic abnormalities[2,3]; thus, it is theorized that interaction between the virus and host genetics may be an important determinant of the natural history of HCV infection and may be predictive of therapy outcome.

A recent genome-wide association study (GWAS) of > 600000 polymorphisms in a cohort of HCV-infected patients found a single nucleotide polymorphism (SNP) on chromosome 19 associated with therapy response[4]. Subsequent GWAS studies implicated the *rs8099917 (*TG) polymorphism in the genetic region of this chromosome related to the interleukin (*IL*)*28B* gene and showed direct associations of the SNP to spontaneous clearance of HCV and treatment outcome[5,6]. Subsequent related studies have identified an additional *IL28B*-related SNP, rs12979860, and confirmed these two polymorphisms as strong predictors of therapy response and contributors to the epidemiological and ethnical distribution of HCV infection[7-9]. In addition, comparative analysis has identified significant differential prevalence profiles of these SNPs for HCV-infected patients and healthy controls[4], suggesting potential roles for each in disease susceptibility and/or resistance.

The prevalence rate of HCV remains high in Brazil, particularly when compared to the other Latin American countries[10], yet little data is available on the genetic variation profile of this disease in Brazilians. This study was designed to analyze the differential genotypic and allelic distributions of the *IL28B*-related SNPs, rs12979860 and rs8099917, in a cohort of Brazilian patients infected with HCV genotype 1 and healthy controls, as well as to investigate the potential association of these polymorphisms with treatment outcome.

## MATERIALS AND METHODS

### Patients

Between January 2010 and January 2012, adult patients who had undergone combination therapy for chronic infection with HCV genotype 1 [48-wk combination of PegIFN-α-2a/2b and RBV (15 mg/kg)] were recruited from the following six large urban healthcare centers: Hospital Municipal São José, Joinville/SC ($n$ = 25); Hospital Universitário Gaffrée Guinle ($n$ = 26) and Hospital Universitário Clementino Fraga Filho ($n$ = 66), Rio de Janeiro/RJ; Hospital da Universidade Federal de Pelotas ($n$ = 12), Pelotas/RS; Santa Casa de Misericórdia ($n$ = 2),

**Table 1 Demographic characteristics of the study participants**

| Characteristic | HCV ($n$ = 145) | Control ($n$ = 198) |
|---|---|---|
| Age (yr), mean ± SD | 55.5 ± 10.0 | 32.2 ± 10.0 |
| Sex, M/F | 52%/48% | 66%/34% |
| Skin color | | |
| White | 75.70% | 88.00% |
| Black | 19.20% | 5.00% |
| Brown | 5.10% | 7.00% |

HCV: Hepatitis C virus.

Porto Alegre/RS; and Hospital da Universidade Federal do Maranhão ($n$ = 14), São Luis/MA. Patients with co-infection of hepatitis B virus or human immunodeficiency virus, or with any other concomitant chronic liver disease, were denied study enrollment. Blood sample and data on treatment outcome was collected for each enrolled patient. The treatment outcome of sustained virological response (SVR) was defined by a negative result for detection of serum HCV RNA at month six post-treatment. Patients who did not achieve SVR (including those who relapsed) were collectively categorized as non-responders (NR).

### Healthy controls

Healthy individuals presenting for blood donation at HEMOSC Joinville/SC in 2010 were recruited for the study. Study enrollment was offered to individuals with no clinical or laboratory evidence of liver disease or other major pathological conditions. All enrolled controls were > 18 years old and lacked familial relationship.

### Racial classification

To phenotypically classify each study participant by race, we employed the criteria published by the Brazilian Institute of Geography and Statistics[11]; the skin color categories (white, brown, black, yellow, and Indian) were self-reported by each participant.

### Ethics statement

The study was approved by each of the participating healthcare center's Institutional Committees, which required adherence to the Brazilian normative for ethics in research. Informed consent was obtained from each participant before blood sampling.

### Genotyping methods

The HCV patients' blood samples were collected by finger puncture and stored as blots on FTA Elute Micro Cards® (Whatman, Kent, United Kingdom) for subsequent genomic DNA extraction according to the manufacturer's protocol. The controls' blood samples were collected by venipuncture and stored in EDTA for subsequent genomic DNA extraction *via* the QIAamp DNA Miniprep Kit (Qiagen, Chatsworth, CA, United States).

The genotyping of SNPs rs12979860 and rs8099917 was performed at the Universidade da Região de Joinville and the Instituto de Biofísica Carlos Chagas Filho. For all 199 control samples and 79 of the HCV-infected samples, genotyping was performed *via* PCR-restriction fragment length polymorphism analysis[12] on an LGC XP thermocycler (BIOER Technology Co., Tokyo, Japan) and results were documented by the Mini-Bis Pro Gel Imaging System (DNR Bio-Image Systems Ltd., Jerusalem, Israel). The remaining 66 HCV-infected samples were genotyped by bi-directional amplicon sequencing using the DYEnamic™ ET Dye Terminator Cycle Sequencing Kit and the MegaBACE 1000 DNA Sequencer (GE Healthcare, Pittsburgh, PA, United States). The HCV treatment responses and *IL28* genotyping results of this subgroup of patients were previously reported[13].

### Statistical analysis

Data analysis was performed by the SPSS statistical software (v13.0; SPSS Inc., Chicago, IL, United States). Continuous variables were compared by Student's $t$-test for parametric variables, or by Mann-Whitney $U$ test for non-parametric distributions. All $P$-values are two-tailed and values < 0.05 were considered statistically significant. The $\chi^2$ G test for "Goodness of Fit" was used to verify whether the proportions of the polymorphisms were unequally distributed between controls and patients or in Hardy-Weinberg equilibrium (HWE). Differences in allele and genotype frequencies between different groups were assessed by Pearson's $\chi^2$ test (with $\chi^2$ test for linear trend when appropriate).

## RESULTS

The demographic characteristics of the HCV-infected patients and healthy controls are summarized in Table 1. SNP rs12979860 genotyping was successful in 142 (97.2%) of the patients and 198 (99.5%) of the controls, and SNP rs8099917 genotyping was successful in all 145 (100%) of the patients and 190 (95.5%) of the controls.

### Genotype and allele distributions among the HCV-infected patients and healthy controls

Analysis of rs12979860 showed that the HCV-infected group had a significantly lower prevalence of the CC genotype (30.3% *vs* control group: 47.4%, $P$ = 0.037) and the C allele (0.53 *vs* 0.69, $P$ = 0.0073) and T allele (0.47 *vs* 0.31, $P$ = 0.0073), but a significantly higher prevalence of the TT genotype (24.8% *vs* 8.9%, $P$ = 0.0009). Analysis of rs8099917 showed that the HCV-infected group had a significantly lower prevalence of the TT genotype (46.2% *vs* control group: 67.4%, $P$ = 0.043) and of the T allele (0.63 *vs* 0.83, $P$ = 0.0009), but a significantly higher prevalence of the GG genotype (20.0% *vs* 1.5%, $P$ = 0.0001) and of the G allele (0.37 *vs* 0.17, $P$ = 0.0008).

Both of the *IL28B* SNPs were in HWE among individuals belonging to the control group (rs12979860, $P$ = 0.7; rs8099917, $P$ = 0.1), but only the rs12979860 SNP was in HWE for the HCV group ($P$ = 0.21). Linkage disequilibrium analysis showed that both SNPs were associated with the controls as well as the HCV-infected patients ($P$ = 0.0001).

**Table 2 Demographic characteristics and clinical parameters of hepatitis c virus-infected patients stratified by response to treatment**

| Feature | SVR ($n$ = 55) | NR ($n$ = 89) | $P$ value |
|---|---|---|---|
| Sex, M/F | 54%/46% | 51%/49% | 0.072 |
| Skin color | | | |
| White | 89% | 70% | 0.032 |
| Black | 11% | 26% | 0.009 |
| Brown | - | 4% | ND |
| ALT in UI/mL, mean (IQR) | 97 (54) | 77 (64) | 0.1 |
| Baseline viral load in UI/mL[1] | | | |
| < 600000 | 47.80% | 49.30% | 0.760 |
| ⩾ 600000 | 52.20% | 50.70% | 0.890 |
| Fibrosis score[2] | | | |
| 0-2 | 63.30% | 49.40% | 0.125 |
| 3-4 | 36.70% | 50.60% | 0.126 |

[1]This parameter was only available for 115 patients [46 of sustained virological response (SVR), and 69 of non-responders (NR)]; [2]According to histopathological analysis of liver biopsy tissues; this parameter was only available for 128 patients (49 of SVR, and 79 of NR). ND: Not done due to small numbers of cases; ALT: Alanine aminotransferase.

### Correlation between the IL28B polymorphisms and treatment outcomes

Fifty-five (39%) of the patients achieved SVR following the combination therapy. Stratification analysis of the SVR patients by race showed that the rate was significantly lower in the self-declared black individuals ($P$ = 0.009). None of the clinical parameters were significantly different between the SVR and NR groups (Table 2). However, the SVR group did have significantly higher prevalences of the rs12979860 CC genotype (45.5% *vs* NR: 21.0%, $P$ = 0.02) and C allele (0.64 *vs* 0.46, $P$ = 0.019). Conversely, the prevalences of the rs12979860 TT genotype and T allele were significantly higher in the NR group (30.0% *vs* SVR: 18.2%, $P$ = 0.03 and 0.54 *vs* 0.36, $P$ = 0.019).

There were no significant differences in the distributions of the SNP rs8099917 genotypes between the SVR and NR groups. However, the SVR group showed a significantly higher frequency of the T allele (0.74 *vs* NR: 0.57, $P$ = 0.024) but a significantly lower frequency of the G allele (0.26 *vs* 0.43, $P$ = 0.024). Linkage disequilibrium analysis of the SVR group only showed a significant association between rs12979860 and rs8099917 ($P$ = 0.07), similar analysis of the NR group only found no significant associations.

## DISCUSSION

Polymorphisms in the genomic sequence related to the *IL28B* gene have been implicated in the natural history of HCV infection and suggested as putative biomarkers for predicting an individual's therapy response[14-17]. In particular, the CC genotype of rs12979860 (*vs* CT) was associated with a two-fold difference in response to HCV treatment, both in Caucasians and African-Americans. Thomas *et al*[18] reported the allele frequencies of rs12979860 in 2371 individuals from 51 populations worldwide, and showed that the C allele occurred at a high frequency in East Asia, an intermediate frequency in Europe and North America, and a relatively low frequency in Africa. In a subsequent study, Fabris *et al*[19] genotyped the *rs12979860* polymorphism in 412 patients with end-stage liver disease due to hepatitis B or C, alcohol abuse, or other causes, and in 344 healthy controls. The patients with viral cirrhosis were found to have a significantly higher frequency of the T allele and of the TT/CT genotypes than the controls; ultimately, the authors theorized that the TT genotype may be associated with severe liver disease while the CC genotype may exert a protective effect. In an Australian-European cohort study of the *rs12979860* polymorphism related to SVR, the TT, TG and GG genotypes were found to be associated[7]. Finally, a Swiss study yielded similar results, with a lower G allele frequency being associated to persistent infection and failure to respond to therapy[6].

Among the few studies that have assessed the role of *IL28B* polymorphisms in a Brazilian population, the SNPs have shown various associations to disease outcome and treatment response. For example, Cavalcante *et al*[20] analyzed rs12979860 in 222 patients infected with admixture HCV genotype 1, 2 and 3 who were treated with standard therapy and found that genotypes CC (rs12979860) and TT (rs8099917) were strongly associated with SVR, while CT/TT (rs12979860) and TG/GG (rs8099917) were associated to treatment failure. In addition, Lunge *et al*[21] analyzed the association between CT (rs12979860) and spontaneous clearance of HCV infection in HIV-co-infected individuals and showed that the CT/TT genotypes conferred nearly 3-fold higher rates for developing CHC, compared to the CC genotype. The current study of *IL28B* polymorphisms' relationship to therapy response, presented herein, confirmed the predictive value of the C allele and CC genotype (rs12979860) that was previously suggested by Cavalcante *et al*[20]. Even though the current study's cohort did not show a statistically significant association of rs8099917 to therapy response, the T allele distribution was related to treatment outcome. This finding may be explained by the lack of HWE in the sample.

Another intriguing finding from the current study is the significant differences in allele and genotype distributions between the healthy controls and HCV-infected patients, which was observed for both SNPs (rs12979860 and rs8099917), with higher C and T alleles as well as CC and TT genotypes in the healthy controls. These data are in accordance with a previous study that demonstrated significant associations for reduced frequencies of the C allele and the CC genotype with chronically-infected hepatitis patients compared to ethnically-matched healthy controls[4]. Together, these findings suggest a strong association between the C allele and higher rates of natural clearance of HCV and support the predicted role of this SNP as a protective factor against HCV infection or persistence.

The full array of biological pathways that are influ-

enced by the *IL28B* gene product and its polymorphisms has yet to be elucidated. Certainly, a gene variant has the ability to affect rates of protein production and it is interesting to consider that Shi *et al*[22] demonstrated that patients with chronic HCV infection have significantly lower mRNA and serum levels of IL28B than either healthy controls or patients who have spontaneously cleared the virus, whereas individuals carrying the rs12979860 CC genotype showed a tendency towards higher levels compared to those carrying the CT or TT genotypes. The SNPs rs12979860 and rs8099917 are located respectively at 3 and 8 kb upstream from the *IL28B* locus, in a region that encodes IFN-λ3, a type 3 interferon with antiviral activity that is mediated through the JAK-STAT pathway upon induction of IFN-stimulated genes. IL28A (IFN-λ2) and IL29 (IFN-λ1) are genomically located adjacent to the *IL28B* gene, and it is possible that the rs*1*2979860 and rs8099917 SNPs may also affect the function of these genes. Indeed, Langhans *et al*[23] showed that IL29 levels were substantially lower in CHC patients and in patients that spontaneously resolved hepatitis, compared to healthy controls; moreover, the levels of *IL29* and *IL28A/B* were shown to be significantly higher in rs12979860 C allele heterozygous patients than in the TT homozygous patients.

The results from the current study of an HCV-infected Brazilian population indicate that the role of *IL28B* SNPs in patients' response to therapy is similar to that of other international populations. Furthermore, the data presented herein on the differential distribution of *rs12979860* and *rs8099917* polymorphisms between HCV-infected patients and a healthy population may contribute to a better understanding of the natural history of this complex disease.

## COMMENTS

### Background

Most countries continue to rely on drug therapies based on an immune-modulator plus an antiviral (most frequently pegylated-interferon α-2a or -2b and ribavirin), even though this strategy is associated with high failure rates and significant side effects. Therefore, identification of predictive biomarkers of an individual's response to therapy is clinically relevant.

### Research frontiers

Since 2009, several genome-wide association studies have yielded data to support the association of two single nucleotide polymorphisms, rs12979860 and rs8099917, located near the interleukin (*IL*)*28B* gene with achievement of sustained virological response to treatment in patients infected with hepatitis C virus (HCV) genotype 1.

### Innovations and breakthroughs

This study represents the largest analysis of a Brazilian cohort conducted to date to investigate the potential association of the two most relevant *IL28B* single nucleotide polymorphisms (rs12979860 and rs8099917) in healthy individuals and chronic hepatitis C patients (CHC) treated with the pegylated-interferon α-2a or -2b plus ribavirin combination therapy. The study's findings reveal significant differential distributions of the genotype and allele frequencies for both rs12979860 and rs8099917 between the healthy controls and CHC patients. In addition, the CC genotype of rs12979860 was shown to be associated with the CHC patients' ability to achieve sustained virological response to the standard therapeutic regimens.

### Applications

This study's findings support the predicted roles of rs12979860 C allele and rs8099917 T allele as protective factors against HCV infection or persistence and suggest their potential for development as clinical biomarkers of HCV infection and therapeutic management. In general, the results indicate that genotyping *IL28B* polymorphisms in HCV-infected patients is likely to help improve the current standard of care, and may provide an opportunity for clinicians to improve patient outcome by individualizing treatment regimens.

### Peer review

The authors investigated the differential distribution of *IL28B* genetic variants between healthy Brazilians in the general population and HCV-infected patients undergoing standard drug therapy based on an immune-modulator plus an antiviral to demonstrate the associations of particular genotypes and alleles with infection and treatment response. This is a well-written and -discussed paper, of particular interest to the Brazil population.

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**P- Reviewer**: Osna NA **S- Editor**: Gou SX **L- Editor**: A
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ISSN 1007-9327
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