IFNL4/IL-28B haplotype structure and its impact on susceptibility to hepatitis C virus and treatment response in the Japanese population

Hidenori Ochi,1,2,3 Daiki Miki,1,2,3 C. Nelson Hayes,1,2,3 Hiromi Abe,1,2,3 Yasufumi Hayashida,1 Michiaki Kubo4 and Kazuaki Chayama1,2,3

Correspondence
Kazuaki Chayama
chayama@hiroshima-u.ac.jp

Received 4 October 2013
Accepted 18 March 2014

A new type III interferon, IFN lambda 4 (IFNL4), and its single-nucleotide polymorphism (SNP) ss469415590 causing a frame shift have been recently reported strongly to affect antiviral therapy for chronic hepatitis C virus (HCV) infection in African and Caucasian populations compared to previously reported IL-28B SNPs rs12979860 and rs8099917. To compare the predictability for treatment outcome among those polymorphisms, we estimated haplotype structure of IFNL4/IL-28B consisting of the three SNPs in 4630 Japanese chronic hepatitis C patients and 1122 healthy controls and then compared their impact on response to pegylated-IFN (PEG-IFN) plus ribavirin (RBV) combined therapy in 903 HCV-1b-infected patients. A total of five haplotypes were identified, although two major haplotypes accounted for 99% of the variation. The SNPs were tightly linked but not in absolute linkage disequilibrium. We could not find any difference in the predictive impact of any of these three SNPs with regard to susceptibility to HCV and treatment response. However, patients with favourable rs8099917 TT, linked to unfavourable genotypes of ss469415590 and rs12979860, showed poor initial viral response compared with those with all favourable genotypes (P=0.0022). These findings suggest that, in part, ss469415590 and rs12979860 may have better predictive impact on response to PEG-IFN plus RBV therapy in the Japanese population, especially in patients with any of the minor haplotypes consisting of these SNPs.

INTRODUCTION

Hepatitis C virus (HCV) infection is the major cause of chronic liver disease, liver cirrhosis and hepatocellular carcinoma. There are more than 180 million HCV chronic carriers worldwide (Chevaliez & Pawlotsky, 2007; Shepard et al., 2005). The current standard of care for the treatment of chronic hepatitis C (CHC) is pegylated-IFN (PEG-IFN) with ribavirin (RBV). However, less than half of patients with HCV genotype 1 achieve a sustained viral response (SVR) with this therapy (Hadziyannis et al., 2004). The addition of direct-acting antiviral (DAA) protease inhibitors, such as telaprevir and boceprevir, to the current standard of care regimen improves the rate of SVR to 65–75% (Morgan & O’Brien, 2011), while entailing increased risk of side effects, including anaemia and rash. Therefore it would be helpful to be able to identify patients who will respond to the current standard of care without DAA agents.

A number of pretreatment predictors of SVR have been reported. HCV genotype, baseline viral load, liver fibrosis, age, sex, obesity, insulin resistance, low-density lipoprotein cholesterol levels and γ-glutamyl transeptidase (γ-GTP) levels have been reported to be associated with the outcome of PEG-IFN plus RBV therapy (Bergmann et al., 2007; Charlton et al., 2006; Gao et al., 2004; Gopal et al., 2006; Romero-Gómez et al., 2005; Zeuzem et al., 1996, 2000).

In addition, both host and viral genetic factors have been implicated in treatment response. Substitutions within the HCV IFN sensitivity determining region (ISDR) (Akuta et al., 2009; Yen et al., 2008) and the IFN/RBV resistance determining region (IRRDR) (El-Shamy et al., 2001).
and a substitution at amino acid 70 of the HCV core protein (Akuta et al., 2006) have also been reported to affect PEG-IFN plus RBV combination therapy. With respect to host genetic factors, recent genome-wide association studies (GWAS) have reported a set of common single-nucleotide polymorphisms (SNPs) near the IL-28B locus on chromosome 19 that are strong predictors of SVR (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009) as well as spontaneous viral clearance (Thomas et al., 2009).

Despite recent research efforts, the true causal variant at the IL-28B locus and the mechanism by which it modulates the IFN response remain unclear. In our previous study using Japanese subjects, we resequenced the region surrounding the locus and found that several known and newly discovered SNPs were associated with virological response (Ochi et al., 2011). One of these, a dinucleotide polymorphism that introduces a frame shift, was recently reported to affect the expression of IFN lambda 4 (IFNL4), a newly identified type III IFN, by causing a frame shift (Prokunina-Olsson et al., 2013). Furthermore, this polymorphism was found to be more strongly associated with the outcome and early viral dynamics of PEG-IFN and RBV therapy than the major IL-28B SNPs, especially in African populations (Prokunina-Olsson et al., 2013).

The aim of this study was to examine how well the IFNL4 polymorphism (ss469415590) can predict viral response in Japanese patients infected with HCV, as compared to IL-28B polymorphisms (rs8099917 and rs12979860) conventionally used for prediction.

### RESULTS

#### Allelic and haplotype frequencies in the Japanese population

No significant deviation from Hardy–Weinberg equilibrium (HWE) was observed either in CHC patients or in healthy controls for any of the SNPs, thus, selection bias or genotyping error was unlikely (Hosking et al., 2004; Salanti et al., 2005). Allelic frequencies of the three SNPs in CHC and control groups are shown in Table 1. The unfavourable allele frequencies of rs12979860, ss469415590 and rs8099917 in CHC patients were higher than those in controls for each SNP ($P=0.001$, $P=0.0007$, $P=0.002$, respectively). However, an integrated discrimination improvement (IDI) test showed that there was no significant difference in the strength of association with CHC (i.e. difference in $P$ value) between any two of the three SNPs. When stratified by HCV genotype, significant differences in favourable allele frequency between HCV-1b patients and healthy controls were found (Fig. 1). By contrast, in the HCV-2a and HCV-2b subgroup, favourable genotype frequency was similar to that of control subjects (Fig. 1).

Linkage disequilibrium among the three SNPs in the studied population is shown in Fig. 2. These SNPs were in strong but not absolute linkage disequilibrium ($r^2=1.0$). Haplotype frequencies in control subjects and CHC patients were estimated and compared using the Haploview program. A total of five haplotypes including two major haplotypes were identified (Table 1). The two major haplotypes accounted for $\geq 99\%$ of the variation in both groups. There were significant differences in haplotype frequencies between

| Table 1. IFNL4/IL-28B polymorphisms and haplotypes in CHC patients and controls |
|---------------------------------|---------------------------------|-----------------|-----------------|
| **Allele** | **Frequency (%)** | **Healthy controls (n=1122)** | **CHC patients (n=4630)** | **P value$^*$** | **P value$^+$** |
| rs12979860 |  |  |  |  |  |
| C | 89.8 | 87.3 | 0.001 | 0.021 |
| T | 10.2 | 12.7 |  |  |
| ss469415590 |  |  |  |  |  |
| TT | 89.9 | 87.3 | 0.0007 | 0.022 |
| AG | 10.1 | 12.7 |  |  |
| rs8099917 |  |  |  |  |  |
| T | 90.2 | 87.9 | 0.002 | 0.021 |
| G | 9.8 | 12.1 |  |  |
| Haplotype$^\ddagger$ |  |  |  |  |  |
| C-TT-T | 89.8 | 87.3 | 0.0008 |  |
| T-AG-G | 9.7 | 12.1 | 0.0013 |  |
| T-AG-T | 0.40 | 0.56 | 0.35 |  |
| G-TT-C | 0.04 | 0.011 | 0.35 |  |
| G-TT-T | 0.08 | 0.0 | 0.04 |  |

$^*$Chi-squared test under allelic model.

$^+$Adjusted by age and sex.

$^\ddagger$Each haplotype represents allele information of the three adjacent SNPs in sequence, i.e. rs12979860-ss469415590-rs8099917.
CHC and control subjects for the two major haplotypes, however, which were similar to results from the single-marker analysis (Table 1).

Association with treatment outcome of PEG-IFN plus RBV therapy for HCV-1b patients

Among HCV-1b patients completing a full treatment course (n=903), allelic frequencies of the IFNL4/IL-28B SNPs in SVR and non-SVR groups are shown in Table 2. The unfavourable allelic frequencies of rs12979860, ss469415590 and rs8099917 in non-SVR patients were higher than those in SVR patients with each SNP \( (P=4.6 \times 10^{-5}, OR = 0.72; P=4.1 \times 10^{-5}, OR = 0.72; P=2.1 \times 10^{-4}, OR = 0.74) \); there was no significant difference for HCV-2a or HCV-2b.

![Fig. 1. Allele frequencies of IFNL4/IL-28B SNPs in CHC patients stratified by HCV genotype. Black bars, rs12979860; white bars, ss469415590; grey bars, rs8099917. Favourable allele frequency of each SNP in HCV-1b was significantly lower than in healthy controls (rs12979860, \( P=4.6 \times 10^{-5} \), odds ratio (OR) 0.72; ss469415590 \( P=4.1 \times 10^{-5} \), OR 0.72; rs8099917, \( P=2.1 \times 10^{-4} \), OR 0.74); there was no significant difference for HCV-2a or HCV-2b.)](image1)

![Fig. 2. Linkage disequilibrium among IFNL4/IL-28B SNPs in a Japanese population. The upper panel shows linkage disequilibrium of the studied population among the IFNL4/IL-28B SNPs. Each value in the box represents \( r^2 \) or \( D' \) calculated by the Haploview program. The lower panel depicts the haplotype structure of IFNL4/IL-28B loci on chromosome 19 from Phase II HapMap Japanese in Tokyo (JPT) genotype data.](image2)
Early virological response in patients with minor haplotypes

IL-28B SNPs have been reported to be associated with early viral kinetics as well as SVR (Thompson et al., 2010). Further, IFNL4 polymorphism ss469415590 has recently been reported to affect HCV RNA decline after 28 days of treatment more strongly than rs12979860 in the African-American population (Prokunina-Olsson et al., 2013). We examined whether there was any difference in the effect of genotype on early viral kinetics among the three SNPs. As shown in Fig. 3, with respect to median HCV RNA decline of the three genotype groups at weeks 2 and 4 of treatment, very similar patterns were observed, and there were no significant differences in the impact of genotypes on early viral decline among the three SNPs.

Next, we focused on patients with minor haplotypes, because these subgroups may provide valuable insights by highlighting differences in the genotype effect on therapeutic response among the SNPs. Among HCV-1b patients having at least one minor haplotype and treated with PEG-IFN plus RBV therapy, including patients who stopped treatment prematurely, 17 patients could be analysed for correlations between viral load change at week 4 and genotypes for each SNP. As shown in Fig. 4, among patients with minor haplotypes, viral load changes in patients with favourable rs8099917 TT linked to unfavourable genotypes of the other SNPs were significantly less than those in patients with favourable genotypes in all the three SNPs (P=0.0022). Likewise, similar correlation coefficients were observed for rs12979860 (r=0.50) and ss469415590 (r=0.50) compared to that of patients with major haplotypes (r=0.46), whereas a negative correlation was observed for rs8099917 (r=-0.32).

These findings suggest that, in the Japanese population, rs12979860 and ss469415590 may provide better predictive ability than rs8099917, especially in patients with minor haplotypes.

DISCUSSION

In this study, we showed that IFNL4 polymorphism ss469415590 and IL-28B polymorphisms (rs12979860 and rs8099917) were in strong linkage disequilibrium with one another in the Japanese population but were not in absolute linkage disequilibrium. We could not find any differences in the overall predictive impact of any of these three SNPs with respect to susceptibility to HCV and treatment response. However, HCV-1b patients with favourable rs8099917 TT, linked to unfavourable ss469415590 TTAG/AGG and rs12979860 CT/TT, showed poor initial viral reduction compared with those with all favourable genotypes.

Recent GWAS from several laboratories (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009) reported that genetic variants within the IL-28B locus were associated with the efficacy of PEG-IFN and RBV combined therapy in patients infected with HCV genotype 1. Subsequently their findings have been replicated in HCV genotypes 2 albeit with a weaker effect (Kawaoka et al., 2011; Mangia et al., 2010) but not in HCV genotype 3 (Bucci et al., 2013; Moghaddam et al., 2011). Further, spontaneous resolution of acute HCV infection has also been shown to be associated with IL-28B polymorphism (Thomas et al., 2009; Tillmann et al., 2010). A number of clinical phenotypes have been found to be associated with IL-28B variants, e.g. necro-inflammatory activity (Abe et al., 2010), fibrosis, steatosis.
**Fig. 3.** Early viral kinetics and IFNL4/IL-28B SNPs. Median HCV RNA decline, compared to the baseline value, at weeks 2 and 4 of PEG-IFN plus RBV treatment are plotted for each of the three IFNL4/IL-28B SNP genotype groups. There were no significant differences in the impact of genotypes on early viral decline among the SNPs.

**Fig. 4.** Comparison of viral load change at week 4 and IFNL4/IL-28B SNPs in patients with minor haplotypes. In 17 patients with minor haplotypes, initial viral load changes at week 4 for each genotype with respect to rs12979860, ss469415590 and rs8099917 are plotted compared with patients with all major haplotypes. Boxes represent the interquartile range (IQR) between first and third quartiles and the line inside represents the median. Whiskers denote the lowest and highest values within 1.5 × IQR and the dots represent the outliers.
haplotypes, patients with favourable rs8099917 TT, linked to unfavourable genotypes of ss469415590 and rs12979860, showed poor initial viral response compared with those with all favourable genotypes ($P=0.0022$) (Fig. 4). IL-28B variants have also been reported to be associated with early viral kinetics during treatment with PEG-IFN plus PBV in HCV genotype 1 patients (Thompson et al., 2010), which is, in turn, a strong predictor of the eventual response to therapy (Davis et al., 2003). Taken together, these findings suggest that ss469415590 and rs12979860 might be a better predictor of treatment outcome than rs8099917, especially in patients with minor haplotypes.

In conclusion, we found no significant difference in overall predictive impact of any of the IFNL4/IL-28B SNPs, rs12979860, ss469415590 and rs8099917, with regard to susceptibility to HCV and treatment-induced clearance. However, taking into account the finding that patients with favourable rs8099917 TT, linked to unfavourable genotypes of ss469415590 and rs12979860, showed poor initial viral response compared with those with all favourable genotypes, ss469415590 and rs12979860 may have better predictive impact on treatment response in the Japanese population, especially in patients with any of the minor haplotypes consisting of these SNPs.

**METHODS**

**Study subjects and design.** A total of 4630 CHC patients who were outpatients of Hiroshima University Hospital and Hiroshima University-affiliated hospitals were included in the study; 1122 healthy control subjects were also included. All patients had elevated serum alanine transaminase levels for more than 6 months and were positive for both anti-HCV antibody and serum HCV RNA. All patients were negative for hepatitis B surface antigen, had no evidence of other liver diseases, and had not received immunosuppressive therapy before enrolment in the study. Fibrosis stage and activity were diagnosed by pathologists at each hospital according to the criteria of Desmet et al. (1994). Subjects received weekly injections of PEG-IFN-$\alpha$-2b at 1.5 $\mu$g kg$^{-1}$ body mass and oral administration of RBV.
for 48 weeks. The dose of RBV was adjusted based on body mass (600 mg for <60 kg, 800 mg for 60–80 kg, 1000 mg for >80 kg). Patients with less than 75% compliance with prescribed doses of PEG-IFN and RBV were excluded from the analysis of association with treatment outcome. Patients were divided into SVR and non-SVR groups based on treatment outcome. SVR was defined as undetectable serum HCV RNA at 24 weeks after completion of therapy, whereas non-SVR patients were still viraemic at this time including transient responders and non-responders. Table 3 lists the demographic features of the subjects. All subjects received a detailed explanation and all gave written informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committee of each participating medical centre, Hiroshima University, and the SNP Research Center, the Institute of Physical and Chemical Research (RIKEN), Yokohama.

The study design is shown in Fig. 5. In both CHC patients and controls, haplotypes of the three IFNL4/IL-28B SNPs (rs12979860, ss469415590 and rs8099917) were estimated. Of these patients, 1151 infected with HCV-1b were treated with PEG-IFN plus RBV. Among those, early viral dynamics data (serum HCV RNA levels at baseline and at week 4 of therapy) were available in 479 patients. A total of 903 patients with HCV-1b were evaluated with respect to treatment discontinuation, whereas non-SVR patients were still viraemic at this time including transient responders and non-responders. Table 3 lists the demographic features of the subjects. All subjects received a detailed explanation and all gave written informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committee of each participating medical centre, Hiroshima University, and the SNP Research Center, the Institute of Physical and Chemical Research (RIKEN), Yokohama.

The study design is shown in Fig. 5. In both CHC patients and controls, haplotypes of the three IFNL4/IL-28B SNPs (rs12979860, ss469415590 and rs8099917) were estimated. Of these patients, 1151 infected with HCV-1b were treated with PEG-IFN plus RBV. Among those, early viral dynamics data (serum HCV RNA levels at baseline and at week 4 of therapy) were available in 479 patients. A total of 903 patients with HCV-1b were evaluated with respect to treatment outcome, after excluding patients with treatment discontinuation, drop out, and insufficient data collection.

**SNP genotyping.** We genotyped each subject for three SNPs on chromosome 19: rs8099917, rs12979860 and ss469415590 (refSNP no. rs368234815). The first two are IL-28B polymorphisms previously reported to be associated with therapy outcome (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009), and the last was recently found to cause a frame shift in the IFNL4 gene (Prokunina-Olsson et al., 2013). Genotyping was performed using multiplex-PCR followed by the Invader assay (Third Wave Technology) as described previously (Ohnishi et al., 2001). Because IFN-lambda family gene sequences are highly homologous, sequence-specific primers were designed to amplify the desired sequence.

**HCV RNA levels.** HCV RNA levels were measured using RT-PCR-based methods (the original Amplicor method, the high-range method, or the TaqMan real-time PCR test). The measurement ranges of these assays were 0.5–850 KIU ml\(^{-1}\), 5–5000 KIU ml\(^{-1}\) and 1.2–7.8 log IU ml\(^{-1}\), respectively. Saturated samples were diluted with PBS and reassayed. All values are reported as log IU ml\(^{-1}\).

**Statistical analysis.** For general statistical analysis, we employed the R statistical package (http://www.r-project.org). Non-parametric tests (chi-squared test, Mann–Whitney U test) were used to detect significant associations. Deviation from HWE was evaluated by the chi-squared test. Discrimination ability between markers was compared using the IDI test under an additive-effect model in a logistic regression (Pencina et al., 2008). All statistical analyses were two-sided, and \(P<0.05\) was considered significant. The Haploview program (Barrett et al., 2005) was used to estimate linkage disequilibrium between SNPs and haplotype construction.

**Table 3.** Demographic characteristics of subjects included in the study

Counts are listed for categorical values and the median and range are reported for continuous variables. \(P_{\text{HWE}}\), \(P\) value for Hardy–Weinberg equilibrium test.

<table>
<thead>
<tr>
<th>CHC patients</th>
<th>((n=4630))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 (7–95) years</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>2472/2158</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.6 (13.9–39.8)</td>
</tr>
<tr>
<td>Alanine transaminase concentration</td>
<td>54 (2–1500) IU l(^{-1})</td>
</tr>
<tr>
<td>(\gamma)-GTP concentration</td>
<td>39 (6–1530) IU l(^{-1})</td>
</tr>
<tr>
<td>Genotype, 1b/2a/2b/others + undetermined</td>
<td>2941/793/453/443</td>
</tr>
<tr>
<td>Fibrosis, F0/F1/F2/F3/F4/undetermined*</td>
<td>37/937/453/443</td>
</tr>
<tr>
<td>Activity, A0/A1/A2/A3/undetermined*</td>
<td>26/859/1260/2442/2241</td>
</tr>
<tr>
<td>Log viral titre†</td>
<td>5.9 (1.2–7.8)</td>
</tr>
<tr>
<td>rs12979860, CC/CT/TT ((P_{\text{HWE}}))</td>
<td>3526/1032/72 (0.72)</td>
</tr>
<tr>
<td>ss469415590, TTTT/TTAG/(\Delta)AG ((P_{\text{HWE}}))</td>
<td>3528/1030/72 (0.75)</td>
</tr>
<tr>
<td>rs8099917, TT/TG/GG ((P_{\text{HWE}}))</td>
<td>3570/996/64 (0.56)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Healthy controls</th>
<th>((n=1122))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43 (14–93) years‡</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>440/682§</td>
</tr>
<tr>
<td>Body mass index</td>
<td>21.5 (14.1–39.2)‡</td>
</tr>
<tr>
<td>rs12979860 CC/CT/TT ((P_{\text{HWE}}))</td>
<td>905/206/11 (0.85)</td>
</tr>
<tr>
<td>ss469415590 TTTT/TTAG/(\Delta)AG ((P_{\text{HWE}}))</td>
<td>907/204/11 (0.90)</td>
</tr>
<tr>
<td>rs8099917 TT/TG/GG ((P_{\text{HWE}}))</td>
<td>912/200/10 (0.79)</td>
</tr>
</tbody>
</table>

*Based on the criteria for histological assessment by Desmet et al. (1994).
†Viral titre was measured in IU ml\(^{-1}\).
‡\(P<0.001\) compared with the chronic hepatitis C group by Mann–Whitney U test.
§\(P<0.001\) compared with the chronic hepatitis C group by chi-squared test.
ACKNOWLEDGEMENTS

The authors thank the subjects who agreed to participate in this study. We also thank the following team members at Hiroshima University Hospital and Hiroshima Liver Study Group for clinical sample collection: Kazuki Chayama, Hidenori Ochi, Hiroshi Aikata, Yoshikazu Kawakami, Hideyuki Hyogo, Michio Imamura, Akira Hiramatsu, Masatake Tsuge, Nobuhiko Hiraga, Tomokazu Kawaoka, Daiki Miki, Yoshio Katamura, Satoe Yokoyama, Daisuke Miyaki, Eisuke Murakami, Hiromi Abe, C. Nelson Hayes and Niu Shi (Hiroshima University); Yasuyuki Aisaka, Nami Mori and Shintaro Takaki (Hiroshima Red Cross Hospital); Makoto Ohbayashi and Hajime Amano (Onomichi General Hospital); Keiji Tsuji and Koji Waki (Hiroshima City Asa Hospital); Toshio Nakanishi and Takahiro Azakami (Miyoshi Central Hospital); Hiroshi Kohno and Hirota Kazuaki (Kure Medical Center); Shiomi Aimitsu and Keitaro Yamashina (Hiroshima General Hospital of West Japan Railway Company); Tomokazu Ishitobi and Yutaka Nabeshima (Chuden Hospital); Kunio Ishida and Michihito Nonaka (Hiroshima General Hospital); Mikiya Kitamoto (Hiroshima Prefectural Hospital); Toru Tamura (Mazda Hospital); Shinsuke Kira (Saiseikai Hiroshima Hospital); Hideaki Kodama (Hiroshima Kinen Hospital); Keiko Arataki (Tsuchiya General Hospital); Hiroyuki Ito (Saiseikai Kure Hospital); Takashi Moriya (Chugoku Rousai Hospital); Eichi Takesaki and Yuko Nagaoka (Higashihiroshima Medical Center); Hiroki Kawakami (Kawakami Clinic); Syuji Yamaguchi (Kure Kyoai Hospital); Hiroto Ishihara (Hiroshima Nishi Medical Center); Toshio Miura (Akutsu Prefectual Hospital); Koji Kamada (Shobara Red Cross Hospital); Ryo Nakashio (Nakashio Clinic); Kazunari Masuda (Masuda Clinic); Masaya Kikkawa (Kikkawa Clinic); Shoichi Takahashi (Koyo New Town Hospital). The authors thank Kana Izumoto and Tomoko Imai for technical assistance and Junko Sakamiya for technical and clerical assistance. This study was supported, in part, by a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour, and Welfare and Ministry of Education Culture Sports Science and Technology, Government of Japan.

REFERENCES


Buic, C., van Delft, A., Christian, A., Fleming, V. M., Harrison, A., Halliday, J., Collier, J., Manganis, C., Kienerman, P. & other authors (2013). ‘Favourable’ IL28B polymorphisms are associated with a marked increase in baseline viral load in hepatitis C virus subtype 3a...


