Regulatory Polymorphisms in the Interleukin-18 Promoter Are Associated with Hepatitis C Virus Clearance

Ping An,1 Chloe L. Thio,2 Gregory D. Kirk,3 Sharyne Donfield,5 James J. Goedert,4 and Cheryl A. Winkler1

1Laboratory of Genomic Diversity, Science Applications International Corporation–Frederick, Frederick, 2Department of Medicine, Johns Hopkins Medical Institutions, and 3Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, and 4Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; 5Rho, Inc., Chapel Hill, North Carolina

The immune response is critical in determining the outcome of hepatitis C virus (HCV) infection. Interleukin (IL)–18 is a pivotal mediator of the Th1/Th2-driven immune response. Two IL-18 promoter polymorphisms (−607C/A and −137G/C) and their haplotypes were known to affect IL-18 expression. We examined the role played by these polymorphisms in determining HCV clearance or persistence. Genotyping was performed among African American injection drug users with HCV clearance (n = 91) or HCV persistence (n = 182) and among European Americans with hemophilia who were mainly infected through plasma transfusion. Among injection drug users, IL18−607A (odds ratio [OR], 3.68 [95% confidence interval {CI}, 1.85–7.34]) and IL18−137C (OR, 2.33 [95% CI, 1.24–4.36]) were significantly associated with HCV clearance. A haplotype carrying −607A and −137C (OR, 4.53 [95% CI, 1.77–11.6]) was also strongly associated with viral clearance. No association was found among those with hemophilia. These results suggest that IL18 promoter polymorphism may affect the outcome of HCV infection in certain groups.

Hepatitis C virus (HCV) infection is one of the most common chronic viral infections in the world. Approximately 80%–90% of acutely infected individuals develop persistent infection, a major risk for the development of liver cirrhosis and liver cancer, whereas a small portion of patients (10%–20%) clear the virus. The interaction between the host defense system and HCV is not well understood, nor are the factors involved in determining viral clearance. It is generally believed that the outcome of acute HCV infection is determined by the competence of the host’s innate and adaptive immune responses. HCV clearance is associated with vigorous HCV-specific CD4+ and CD8+ T cell responses [1–3]. By contrast, lack of a sustained HCV-specific T cell response is associated with the development of persistent infection [3]. It is therefore plausible that host genetic factors that control the immune responses may play a critical role in determining the outcome of HCV infection.

Host genetic factors that have been implicated in HCV infection or persistence mainly include certain alleles in HLA class I and II and cytokine genes [4–9]. Cytokines play an indispensable role in regulating immune responses that control HCV clearance or persistence and the resulting pathogenesis. Genetic polymorphisms of the cytokine genes IFNG (interferon, gamma), TNFA (tumor necrosis factor [TNF], alpha), IL10 (interleukin [IL]–10), and IL19/20 (IL–19/20) have been implicated in determining the outcome of HCV infection [7–9].

IL-18, a proinflammatory cytokine, is an important regulator of innate and acquired immune response. IL-18 is involved in both Th1 and Th2 immune responses, depending on the immunological milieu. In the...
presence of IL-12, IL-18 stimulates IFNG expression, promoting the Th1-mediated immune response; without IL-12, IL-18 stimulates Th2 responses. IL-18 plays a critical role in the host defense against infection with intracellular microbes, and, on the other hand, in inducing autoimmune diseases and propagating inflammatory process [10, 11]. IL-18 is significantly up-regulated in persons with chronic HCV infection compared with healthy persons or asymptomatic carriers, and its higher level is correlated with hepatic injury [12–15], indicating a key role for IL-18 in the pathogenesis of HCV infection. Two single-nucleotide polymorphisms (SNPs) (−607C/A and −137G/C) in the promoter region of the IL18 gene have been repeatedly found to be associated with the IL18 promoter transcription activity [16–19]. Lower promoter activity was observed for the minor alleles −607A and −137C than for the more common alleles −607C and −137G, respectively. Haplotypes carrying these alleles also correlated with IL-18 levels in peripheral blood mononuclear cells or plasma [16, 19, 20]. Moreover, these haplotypes capture the majority of genetic variation in IL18, due to the presence of strong linkage disequilibrium among polymorphisms in the gene [21, 22]. These SNPs have been implicated in various immune disorders, such as type I diabetes, asthma, and rheumatoid arthritis [21, 23, 24].

Because IL-18 is an important immune regulator involved in the pathogenesis of HCV infection, we hypothesized that promoter polymorphisms known to modulate IL18 expression and protein levels may influence the outcome of HCV infection. In this study, the role played by the IL18 promoter polymorphisms −607C/A and −137G/C and their haplotypes was examined in European American (EA) and African American (AA) individuals with well-defined outcomes of HCV clearance or persistence.

**METHODS**

**Study participants.** Study participants were enrolled in 1 of 3 US-based studies of the natural history of HIV-1: (1) the AIDS Link to the Intravenous Experience (ALIVE) Study, comprising a community-based cohort of intravenous injection drug users in Baltimore, Maryland, enrolled in 1988–1989 [25]; (2) the Hemophilia Growth and Development Study, a multicenter prospective study that enrolled children with hemophilia who received blood products in 1982 and 1983 [26]; or (3) the Multicenter Hemophilia Cohort Study, comprising a prospectively monitored cohort of persons with hemophilia enrolled in 1982–1986 [27]. Informed consent was obtained from all participants, and the study was approved by the institutional review boards of all participating institutions.

**Study design.** A nested case-control design was used in which 1 person with viral clearance (case patient) was matched to 1 or 2 persons with viral persistence from the same cohort (control subjects) [7]. The matching criteria were HIV-1 status, sex, geographic location, and ethnicity. The mean age at study entry was similar in the case and control groups (table 1). In the AA group, all case patients had 2 matched control subjects, whereas, in the EA group, only 1 matched control subject was available for some case patients. All participants in the cohorts who were tested for and cleared HCV were included as the case patients. Prior infection was defined as detection of HCV anti-
body by EIA and recombinant immunoblot assay (RIBA). Case patients with HCV clearance were those who had cleared viremia without any HCV-specific treatment, demonstrated by detection of anti-HCV (confirmed by RIBA) and undetectable HCV RNA in the serum for \( \geq 6 \) months. Persistently infected individuals had detectable anti-HCV and HCV RNA in serum for \( \geq 6 \) months.

**Serologic testing.** Participants who tested positive for anti-HCV by the second-generation Ortho HCV EIA (version 2.0; Ortho Diagnostic Systems) had 1 sample assessed for HCV RNA by a branched DNA (bDNA) assay (Quantiplex HCV RNA 2.0; Chiron). Participants with a negative bDNA assay result had a second sample, separated by a minimum of 6 months after the first, tested for HCV RNA with the HCV COBAS AMPLICOR system (Roche Diagnostics), and their antibody status was confirmed by RIBA (RIBA 3.0; Chiron). The limits of viral detection for the bDNA and the COBAS assays are \(-200,000\) equivalents/mL (30,000 IU/mL) and 100 copies/mL (50 IU/mL), respectively. Only subjects with a negative HCV RNA COBAS assay result were defined as having viral clearance. Participants with 2 positive bDNA assays were defined as having a persistent HCV infection. Individuals with negative bDNA and positive COBAS results were not included in this study. HIV-1 testing was done by EIA, and positive specimens were confirmed by Western blot analysis, as described elsewhere [25–27].

**Genotyping.** SNPs at position \(-607C/A\) (dbSNP accession number rs1946518) and \(-137G/C\) (rs187238) in the promoter region of the *IL18* gene were genotyped by polymerase chain reaction (PCR) restriction fragment–length polymorphism assays. The primers were designed on the basis of the GenBank sequence AB015961. The \(-607\) site was amplified using primers 5’-ttctgttgcagaaagttaaatTt-3’ and 5’-aaaggatagttgatacagggcatt-3’, and the \(-137\) site was amplified using primers 5’-tgctttcaagtgaagaggtg-3’ and 5’-cttcttttaatgtaatatcactattttca-tga-Ga-3’, respectively (the capitalized nucleotides were artificially introduced to create the restriction enzyme site). PCRs were performed in a final volume of 20 \( \mu \)L consisting of 50 mmol/L KCl, 10 mmol/L Tris-HCl (pH 8.3), 2.5 (for \(-607\)) or 3.5 (for \(-137\)) mmol/L MgCl\(_2\), 0.25 mmol/L dNTP, 25 ng of DNA, 1.25 U of TaqGold polymerase (Applied Biosystems), and 0.20 \( \mu \)mol/L each forward and reverse primer.

At the first PCR cycle stepping, denaturation was performed at 95°C for 10 min. This was followed by 35 cycles of 94°C for 30 s, 58°C for 30 s, and 72°C for 45 s; final extension was at 72°C for 7 min. The PCR products were digested with the appropriate restriction enzymes (New England Biolabs) overnight and then separated on 4% agarose gels. For the \(-607\) site, the product sizes digested with *DraI* were 154 bp for the C allele and 125 and 28 bp for the A allele. For the \(-137\) site, the product sizes digested with *BglII* were 105 and 36 bp for the G allele and 141 bp for the C allele. The samples from case patients and control subjects were randomly distributed in the plates. Two water controls were included on each 96-well plate. Approximately 70% of all samples were independently genotyped twice. The persons performing the genotyping were blinded to the clinical data. The genotypes obtained were free of water contamination or inconsistencies between duplicate DNA samples.

**Statistical analyses.** Statistical testing was conducted using the SAS package (version 9.1; SAS Institute). Haplotype frequencies and linkage disequilibrium estimates between the 2 SNPs were evaluated by a maximum likelihood method using the expectation maximization algorithm [28]. For the SNP and haplotype analyses, a conditional logistic regression analysis was used for the matched case-control comparison for the dominant genetic model, comparing those carrying 1 or 2 minor alleles with those homozygous for the major frequency allele. The association with HCV load at study entry was evaluated by Student’s *t* test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated; ORs >1 indicate a protective association with HCV clearance. *P* values are 2 sided.

**RESULTS**

To determine the effect of IL-18 on HCV clearance, we examined the 2 *IL18* promoter SNPs at \(-607\) and \(-137\) in 2 case-control groups consisting of either AA participants (91 case patients with HCV clearance and 182 control subjects with chronic infection) or EA participants (106 case patients with HCV clearance and 192 control subjects with chronic infection) (table 1). Because the allele frequencies of these 2 SNPs differ in the 2 populations, the analysis was performed separately for the AA and EA groups. Genotype frequencies for each SNP conformed to Hardy-Weinberg expectations in the control groups.

Among AA patients, both promoter SNPs, \(-607C/A\) and \(-137G/C\), showed differences in frequency distributions between the HCV clearance and persistence groups (table 2). The \(-607A\) allele occurred more frequently in the clearance group (0.439) than in the persistence group (0.335). The \(-137C\) allele was also more frequently observed in the clearance group (0.269) than in the persistence group (0.195). In a dominant genetic model, the genotypes carrying 1 or 2 copies of \(-607A\) (OR, 2.92 [95% CI, 1.59–5.36]; *P* < .001) or \(-137C\) (OR, 2.09 [95% CI, 1.20–3.65]; *P* = .009) were associated with clearance of HCV infection. Among EA patients, genotypes containing these variant alleles did not differ in frequency distribution between the 2 groups. Because hepatitis B surface antigen (HBsAg) was more common in the HCV clearance group than in the persistence group (table 1), the HBsAg status was adjusted for in the logistic regression analysis. After adjustment for HBsAg status, the effects of \(-607A\) (OR, 3.68 [95% CI, 1.85–7.34]; *P* < .001) and \(-137C\) (OR, 2.33 [95% CI, 1.24–4.36]; *P* = .024) became stronger (table 2).

As a means of validating the observed frequencies, we checked the allele frequency of IL-18 SNPs in the general population.
Among the 48 chromosomes of AA persons and 40 chromosomes of EA persons genotyped in the Coriell human variation panel available from dbSNP, the allele frequencies are 0.354 and 0.425, respectively, for −607A and 0.15 and 0.30 for −137. The frequencies in this unselected population are mostly similar to those observed in the HCV persistence group, consistent with the expectation that HCV persistence is much more common than clearance.

Haplotypes formed by the variants −607C/A and −137G/C were reconstructed by the expectation maximization method. A near-complete linkage disequilibrium existed between these 2 variants ($D^' = 0.99; r^2 = 0.49$). Three 2-locus haplotypes (CG, AC, and AG) were present in both the clearance and the persistence group (table 3). Compared with the reference homozygous GC haplotype, the AG and AC haplotypes were elevated in the HCV clearance group. AC was found to be strongly associated with HCV clearance (OR, 2.67 [95% CI, 1.23–4.16]; $P = .004$). AG was also associated with HCV clearance, with marginal significance (OR, 2.50 [95% CI, 1.04–6.04]; $P = .04$).

### Table 2. **IL18** promoter polymorphisms in persons with hepatitis C virus (HCV) clearance or persistence.

<table>
<thead>
<tr>
<th>Group, SNP</th>
<th>Allele frequency</th>
<th>Haplotype frequency</th>
<th>Unadjusted</th>
<th>Adjusted for HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clearance</td>
<td>Persistence</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>AA patients</td>
<td>n = 182</td>
<td>n = 364</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−607A</td>
<td>0.439</td>
<td>0.335</td>
<td>2.92 (1.59–5.36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>−137C</td>
<td>0.269</td>
<td>0.195</td>
<td>2.09 (1.20–3.65)</td>
<td>.009</td>
</tr>
<tr>
<td>EA patients</td>
<td>n = 212</td>
<td>n = 384</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−607A</td>
<td>0.41</td>
<td>0.42</td>
<td>0.89 (0.54–1.47)</td>
<td>.64</td>
</tr>
<tr>
<td>−137C</td>
<td>0.276</td>
<td>0.29</td>
<td>0.89 (0.55–1.46)</td>
<td>.65</td>
</tr>
</tbody>
</table>

NOTE. Odds ratios (ORs) are for having HCV cleared compared with having persistent HCV infection when carrying 1 or 2 copies of −607A or −137C. Analyses were performed using conditional logistic regression with or without adjustment for hepatitis B surface antigen (HBsAg) status. $n$ indicates the no. of alleles. AA, African American; CI, confidence interval; EA, European American; SNP, single-nucleotide polymorphism.

### Table 3. **Haplotype distribution of 2 IL18** promoter polymorphisms in persons with hepatitis C virus (HCV) clearance or persistence.

<table>
<thead>
<tr>
<th>Group, haplotype</th>
<th>−607C/A</th>
<th>−137G/C</th>
<th>Haplotype frequency</th>
<th>Unadjusted</th>
<th>Adjusted for HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clearance</td>
<td>Persistence</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>AA patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CG</td>
<td>C</td>
<td>G</td>
<td>0.561</td>
<td>0.663</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>AC</td>
<td>A</td>
<td>C</td>
<td>0.267</td>
<td>0.193</td>
<td>3.15 (1.45–6.87)</td>
</tr>
<tr>
<td>AG</td>
<td>A</td>
<td>G</td>
<td>0.172</td>
<td>0.144</td>
<td>2.5 (1.04–6.04)</td>
</tr>
<tr>
<td>EA patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CG</td>
<td>C</td>
<td>G</td>
<td>0.580</td>
<td>0.575</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>AC</td>
<td>A</td>
<td>C</td>
<td>0.277</td>
<td>0.288</td>
<td>0.94 (0.51–1.73)</td>
</tr>
<tr>
<td>AG</td>
<td>A</td>
<td>G</td>
<td>0.134</td>
<td>0.138</td>
<td>0.9 (0.37–2.22)</td>
</tr>
</tbody>
</table>

NOTE. Odds ratios (ORs) are for having HCV cleared compared with having persistent HCV infection for the specific haplotype; ORs and 95% confidence intervals (CIs) were calculated for each of 2 haplotypes (AC and AG) excluding the other haplotype relative to the homozygous CG haplotype, using conditional logistic regression with or without adjustment for hepatitis B surface antigen (HBsAg) status. AA, African American; EA, European American.
patients, with broadly overlapping 95% CIs. Similar results were observed for the haplotypes (OR for haplotype AC for HIV-1 positive vs. negative, 3.96 [95% CI, 1.07–14.61] vs. 2.75 [95% CI, 1.04–7.29]; OR for haplotype AG for HIV-1 positive vs. negative, 2.26 [95% CI, 0.54–9.37] vs. 2.57 [95% CI, 0.86–7.67]). These explanatory analyses indicate that the observed effects were not confounded or influenced by HIV-1 infection.

The potential impact of IL18 SNPs on HCV load was assessed in the HCV persistence control group. Among AA patients, the mean ± SD HCV RNA level at study entry was 6.85 ± 0.72 log_{10} copies/mL in the referent homozygous CG haplotype group and was slightly (nonsignificantly) lower in the haplotype AC (6.75 ± 0.81 log_{10} copies/mL; P = .44) and AG (6.68 ± 0.87 log_{10} copies/mL; P = .26) groups. Among EA control subjects, the HCV RNA levels were measured at 6.44 ± 0.74, 6.38 ± 0.73, and 6.53 ± 0.75 log_{10} copies/mL in these 3 groups (P > .5), respectively.

**DISCUSSION**

Clinical outcomes of HCV infection are determined by the interplay among the host immune response and viral and environmental factors. By comparing patients who either had persistent HCV infection or had cleared HCV infection, the present study demonstrated that 2 functional promoter variants (−607C/A and −137G/C) in the IL18 gene were associated with clearance of HCV infection in AA but not EA patients. A haplotype (AC) carrying both −607A and −137C was strongly associated with HCV clearance (OR, 4.53). This finding points to a critical role for IL-18 in determining the outcome of HCV infection.

From individual SNP analysis, both −607A and −137C were associated with clearance of HCV infection, with the effect of −607A being stronger. Among 3 haplotypes observed, haplotype AC was significantly associated with HCV clearance, whereas AG showed a tendency toward association with clearance, also suggesting a broader effect of −607A than of −137C. Whether the −137C allele confers an independent effect is difficult to determine, because −137C is tracking −607A.

Promoter SNPs −607 and −137 modulate IL18 gene expression through alteration of nuclear factor binding sites. A change from C to A at site −607 disrupts a binding site of CAMP-responsive element, which mediates transcriptional activation in response to CAMP [29], resulting in low IL-18 production. The −137G/C SNP is located on the binding sites of the Th2-specific transcription factor GATA binding protein 3 [30], human histone H4 gene–specific transcription factor 1, and hepatocyte nuclear factor–3B (forkhead box A2), a liver-enriched transcriptional activator for liver-specific transcripts [31, 32], suggesting that potential differential regulation of IL18 in hepatocytes is afforded by −137 alleles. Zhou et al. [19] demonstrated that the promoter sequence with haplotype AG exhibits lower promoter activity than does that with CG and that −607A is associated with lower serum IL-18 levels than −607C. Monocytes from −137C carriers produce less IL-18 than do those from −137G carriers [18]. Giedraitis et al. [16] found that haplotypes CG and AG have higher transcription activity than does haplotype AC. In light of these studies of promoter activity, the more common alleles associated with HCV clearance, −607A and −137C, or haplotype AC would be predicted to exhibit low promoter activity. The AC haplotype has been associated with atopic eczema and asthma, which are classified as Th2-dominant diseases [21, 33, 34]. Our finding that the AC haplotype is associated with viral clearance suggests that the same genetic variation may increase the risk for one group of disorders but protect against other types of diseases, such as infection.

The genetic epidemiological results point to an important role for IL-18 in the pathogenesis of HCV infection. The mechanisms may involve both the immunoregulation function and the inflammation-inducing effect of IL-18. It is believed that the dynamics of the Th1/Th2 response determine the outcome of HCV infection and that IL-18 is an important mediator of Th1/Th2 balance. Thus, it is plausible to reason that down-regulation of IL-18 by these promoter SNPs help to achieve an optimal balance of Th1 and Th2 in favor of HCV clearance. There is evidence that low production of IL-18 contributes to viral clearance [35]. In a study of mice after pulmonary infection with influenza A virus, IL18 deficiency was found to be associated with accelerated viral clearance of influenza A virus and enhanced activation of CD4+ T cells [35]. Furthermore, in a comparison of patients with chronic hepatitis B and normal control subjects, haplotype AC of IL18 was found to be associated with protection against HBV infection [36]. This corroborates our finding of an association between haplotype AC and HCV clearance and suggests that these IL18 SNPs share a common role in viral hepatitis. A related issue is whether IL-18 SNPs affect HCV load. A nonsignificant reduction of 0.1 or 0.17 log_{10} HCV RNA copies/mL was observed in the AC and AG haplotype groups compared with the CG haplotype group among the AA patients with HCV persistence, suggesting a possible HCV inhibitory effect. However, given that the duration of HCV infection in these patients is unknown, further studies on this aspect are needed to draw any conclusions.

On the other hand, IL-18, as a proinflammatory cytokine, directly induces inflammation in liver cells. In animal experiments, IL-18 and TNF-α have been identified as essential mediators of T cell–mediated liver injury [37]. The simultaneous neutralization of TNF-α and IL-18 fully protected mice against hepatic damage induced by exotoxin [38]. A neutralizing antibody to IL-18 completely prevented lipopolysaccharide-induced hepatic damage [39]. In clinical studies, IL-18 was found to be up-regulated during chronic hepatitis C and to be related to hepatic injury [12–15]. A lower level of IL-18 production mod-
ulated by −607A may help protect hepatocytes from persistent inflammation induced by HCV.

In the present study, the effect of IL-18 variants on HCV clearance was observed in AA patients but not in EA patients. In a recent review of meta-analyses of 43 validated genetic associations, Ioannidis et al. [40] found that 15 analyses achieved statistical significance in 2 racial groups. Regardless of whether the differences achieved significance, in 32 studies the genetic effects, as estimated by ORs, were in the same direction across different racial groups. In the present study, the lack of a positive association in EA patients may be related to the initial HCV inoculum, immune response, or genetic background. More than 90% of the AA patients were exposed to HIV-1 through needle sharing and presumably received a small HCV inoculum, whereas >90% of EA patients had hemophilia and were exposed to a large HCV inoculum by plasma infusion. It is possible that a large inocula of HCV may overwhelm the host’s immune system such that the beneficial role of genetic IL18 modulation is minimized. Alternatively, it is possible that small inocula may lead to a more efficient immune response. Khakoo et al. [4] reported a similar differential effect for HLA-KIR genotypes, where KIR2DL3:HLA-C1 homozygosity was strongly protective in patients infected through needle injection but not in patients infected through blood transfusions [41].

The distinctive genetic effects may also be due to the difference in genetic background. It is well known that AA and EA patients differ in the rate of HCV clearance and treatment response [42, 43]. Recent studies presented biological evidence that may explain the differential epidemiological effects observed in different racial/ethnic groups. Through immunological analysis of a large number of patients who resolved HCV infection or had persistent HCV infection, EA and AA patients were found to differ in their CD4 T cell responsiveness to HCV antigens [42]. The ability of HCV proteins to induce IL-10 production differed in mononuclear cells from AA or EA donors carrying the same IL-10 promoter variants that predict IL-10 levels [44]. Thus, it is not unlikely that the production of IL-18 and induction of immune response from the same genetic variation may differ among groups with different genetic backgrounds. Future replication in other independent samples and evaluation of functional relevance will help address these issues.

The strengths of the present study include the use of a nested case-control design of case patients and control subjects selected from well-characterized longitudinal cohorts, controlling for factors known to influence outcomes by case-control matching on age and HIV-1 status, and the robust association with the clearance phenotype of SNPs with known function. There are limitations to the study. First, the positive association was found only in the AA group. Second, we cannot exclude the possibility that the −607 and −137 effects are tracking other alleles in the IL18 gene, since there is strong linkage disequilibrium within the gene.

In summary, the present study suggests that 2 promoter polymorphisms in the IL18 gene influence the outcome of HCV infection, with the −607A and −137C alleles and their haplotype favoring HCV clearance. These findings highlight a critical role for IL-18 in resolving HCV infection. Because these SNPs are quite common, their impact on the HCV epidemic may be significant. These 2 alleles have been associated with lower levels of IL-18 expression, suggesting that higher levels of IL-18 promote the persistence of HCV infection. If these results are validated, IL-18 could be considered as a target for therapeutics.

Acknowledgments

We thank Yuchun Zhou and Beth Binns-Roemer for excellent technical assistance. We thank 2 anonymous reviewers for valuable suggestions.

References


