Polymorphism in the Human Major Histocompatibility Complex and Early Viral Decline during Treatment of Chronic Hepatitis C

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The dynamics of the viral decline immediately after the start of therapy for chronic hepatitis C virus (HCV) infection may have prognostic potential for ultimate sustained virologic response. Considerable interindividual variability in the decline has been reported, including differences by race. The major histocompatibility complex (MHC) genes encode the human leukocyte antigens, which are important in the immune response to viral infections. We examined whether carriage of specific human MHC alleles are associated with the rate of the early viral decline. Longitudinal viral level data (baseline and days 1, 2, 7, 14, and 28 of treatment), medium resolution MHC genotyping, and random coefficients models were used to examine associations between MHC class I and class II allele carriage and the dynamics of the viral decline in 180 African-Americans (AAs) and 194 Caucasian Americans (CAs) with genotype-1 HCV infection over the first 28 days of treatment with peginterferon α2a plus ribavirin. Baseline viral levels were similar by race, irrespective of allele carriage. However, the rate of change in the viral decline was associated with both allele and race. Among the four subgroups defined by race and specific allele, the fastest rates of decline were observed (in terms of estimated mean viral declines log10 IU/ml during the first four weeks) in CA noncarriers for A*03 (2.75; P = 0.018), in CA carriers for Cw*03 (2.99; P = 0.046), and in CA noncarriers for DQA1*04 (2.66; P = 0.018) or DQB1*0402 (2.65; P = 0.018). MHC alleles are associated with the viral decline during the first 28 days of peginterferon therapy.

Hepatitis C virus (HCV) infection affects an estimated 170 million individuals worldwide and 4 to 5 million in the United States and may result in cirrhosis of the liver and primary hepatocellular carcinoma (2). Currently, therapy for chronic HCV infection consists of a combination pegylated alpha interferon in combination with the nucleoside analogue, ribavirin, and is effective in eliminating virus from ca. 50 to 80% of those treated (8, 20). Significant racial disparities also exist, with African-Americans (AAs) having significantly lower response rates than those of Caucasian Americans (CAs) (5, 12, 13).

Early disappearance of viremia during the first 4 weeks after the start of treatment is believed to be highly predictive of the ultimate sustained response to antiviral therapy. In a recent study, 91% of individuals who were PCR negative for HCV-RNA by week 4 achieved sustained virologic response (SVR), whereas only 60% of patients who had a \(<2\log_{10}\) drop in HCV levels by week 4 but were PCR negative for HCV by week 12 achieved SVR (7). The importance of the early viral response is further underscored in studies of the kinetics of viral decline, where multiple and very frequent measurements of HCV levels are obtained during the initial hours after the start of treatment (9, 19). Rapid rates of viral decline are associated with SVR (undetectable levels of HCV 6 months after discontinuation of therapy). Accordingly, viral dynamics may serve as a potential predictor of SVR (18, 19). Racial differences have also been reported with respect to viral dynamics, with AAs exhibiting slower viral dynamic declines than CAs (16, 17). The mechanisms behind the different dynamics of the viral decline are not known, but host genetic variation may contribute.

Spontaneous clearance of HCV is associated with vigorous and robust CD4+ and CD8+ T cells (3), and several studies have indicated an important role for T cells in antiviral therapy-induced clearance (6, 26, 28), although other studies have failed to find an association (14). The genes of the major histocompatibility complex (MHC) encode the highly polymorphic human leukocyte antigens (HLA), which are crucial in antigen presentation and mediation of the T-lymphocyte response. Studies of the potential role of host genetic diversity and the dynamics of the early viral decline have been hampered by the difficulty in obtaining sequential HCV viral levels in a large cohort of individuals. We took advantage of the
availability of repeated viral level data from a clinical study of AA and CA patients undergoing anti-HCV therapy and examined whether carriage of specific MHC alleles is associated with the dynamics of the HCV viral decline during the first 28 days of peginterferon therapy for chronic HCV and whether host genetic factors are associated with differences in viral dynamics by race.

**MATERIALS AND METHODS**

**Study population.** This study utilized participants from the Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C), a multicenter study sponsored by the National Institutes of Health aimed at understanding the mechanisms of resistance to antiviral therapy for chronic HCV infection among interferon treatment-naïve individuals infected with genotype 1 HCV (1a and 1b), as well as the differences in outcome by race among AAs and CAs (5). All subjects were born in the United States, and race was determined by a self-administered questionnaire.

**MHC genotyping.** Genotyping of class I MHC A, B, and C loci and the class II loci, DRB1, DQAI, DBQ1, DPB1, and DPA1, were conducted by using restriction fragment length polymorphism methods with biotin-labeled PCR primers and hybridization of the labeled amplicons to sequence-specific oligonucleotide probes immobilized on nylon membranes developed by Roche Molecular Systems. All typing of MHC genes were conducted by Roche Molecular Systems (Alameda, CA).

**HCV viral assessment.** Viral levels were assessed for all participants in the study at baseline, as well as day 1, 2, 7, 14, and 28 after the initiation of treatment. Although more sensitive assays have been subsequently developed, the Roche HCV Amplicor version 2 assay, which has a lower detection limit of 600 copies/ml, was used in the present study.

**Evaluation of population structure.** Using data from 161 ancestry-informative single nucleotide polymorphisms, we derived estimates of individual admixture for participants in the genetics study and utilized the structured association method developed by Pritchard et al. (23, 24) to evaluate the population structure. We observed two distinct ancestral groups that had a strong correlation with self-reported race (30). Consequently, we used self-reported race in these analyses. We observed two distinct ancestral groups that had a strong correlation with self-reported race (30). Consequently, we used self-reported race in these analyses.

**Statistical analysis.** Carriage of MHC alleles that occurred with a frequency of ≥5% in either racial group was assessed for the potential effect on the change in viral decline during at baseline and days 1, 2, 7, 14, and 28 after the start of treatment (4, 27).

All viral level measurements were log10 transformed to approximate a normal distribution. Due to the fact that the Roche Amplior assay has a lower limit of detection of 600 IU/ml, we imputed the viral level values for those below detectable using a uniform distribution in the log scale. The time variable was expressed as “weeks” (rather than days or hours) in our analyses. A square-root transformation was applied to the time variable to attain linearity.

Longitudinal analysis was conducted using a multilevel model for change (also known as a linear random coefficients model or linear growth model) (4, 27). Detailed mathematical representations of the model are available online in Table S1 in the supplemental material, along with the variance components (see Table S2 in the supplemental material). Briefly, a two-level modeling strategy was utilized; a level 1 submodel describes how each person changes over time, and a level 2 submodel relates “interindividual differences in change” to predictors such as allele carriage and race. A multilevel modeling was chosen because the primary question of interest was to determine whether allele and/or race had an effect on the rate of change in viral levels over time (the dynamics of viral decline). We also adjusted for potential confounding factors such as patient age, sex, fibrosis score ( Ishak ≥ 3 [versus ≤3]), and weight, which we have previously reported to be associated with the interferon response (5). Since these variables did not significantly change our final qualitative conclusions, we omitted them from the final models for the simplicity and focused on the effects of allele and race only. By fitting each “patient” as a random effect, we accounted for the interindividual variability of viral levels at the baseline (i.e., to allow intercepts to vary between patients) “patient-by-time interaction” as a random effect to account for the interindividual variability in rates of change of viral levels (i.e., to allow slopes of the decline to vary between patients) during the course of the first 28 days of therapy. The variables “time,” “allele,” and “race” were included as fixed effects. To evaluate the differential effects of time on HCV RNA by race and allele (i.e., statistical interactions), we also included “race-by-time,” “allele-by-time,” “race-by-allele,” and “allele-by-race-by-time interaction” as fixed effects.

The SAS v.9.1 system (Proc Mixed; SAS Institute, Cary, NC) was used for data analyses, and the R v.2.3.1 statistical package was used for graphical presentation of data (R Language and Environment for Statistical Computing [www.r-project.org]). Statistical significance was set at α = 0.05.

**RESULTS**

**Cohort characteristics.** Of the 401 individuals who were treated in the Virahep-C study (5), 373 consented to participate in host genetics studies (30). Table 1 summarizes the baseline characteristics of the participants in the present study. The distribution of viral levels at baseline, and days 1, 2, 7, 14, and 28 pre- and posttransformation are presented in Fig. 1.

Twenty-four patients required an alteration in the dose of interferon due to side effects. We conducted our analyses with these individuals included, as well as with them excluded, and observed no significant differences in the results. Therefore, we report data with these 24 patients included.

**MHC allele carriage and the dynamics of viral decline.** We observed a total of 47 alleles in our cohort with a frequency of ≥5%. These alleles, along with their corresponding frequencies, are presented in Table 2. Of the alleles tested, four were significantly associated with the dynamics of the viral decline (P < 0.05). The models and results presented in Table 3 evaluate the effects of allele carriage on the initial baseline viral level, as well as on the rates of change in viral levels, over time, controlling for the effects of race.

Based on the two-level model including DQA1*04 allele, the estimated difference between initial viral levels for the noncarriers and carriers of this allele was (−0.08 log10 IU/ml; P = 0.574; Table 3) and AAs had slightly lower baseline viral level than for the CAs by (−0.03 log10 IU/ml; P = 0.756; Table 3). Nonetheless, these differences were not...
statistically significant. This model also estimated the population initial mean viral level to be 6.27 log_{10} IU/ml with a standard error of 0.146. The results were similar for all four models in Table 3, in that allele carriage did not have a significant impact on baseline viral levels between carriers and noncarriers, either independently or when adjusted for race.

However, we did observe differences in the dynamics of the viral decline (Table 3). For DQA1*04 allele carriage, the rate of viral decline was higher among noncarriers than carriers ($P < 0.001$) and the magnitude of the rate of decline depended on race (Table 3 and Fig. 2A). The estimated mean viral level declines for the first 4 weeks were 2.66 for CA noncarriers, 1.51 for AA noncarriers, 1.19 for AA carriers, and 0.98 for CA carriers ($\log_{10} IU/ml, P = 0.018$, Fig. 2A), suggesting that CA noncarriers exhibited the fastest decline. This trend was similar when we examined the estimated mean viral level decline during the first week (Fig. 2A).

The effect of DQB1*0402 was very similar to that of DQA1*04; CA noncarriers exhibited the fastest decline (Fig. 2B) and had higher rates of viral decline compared to carriers. The estimated mean viral level declines during the first 4 weeks were: 2.65 for CA noncarriers, 1.49 for AA noncarriers, 0.94 for CA carriers, and 1.21 for AA carriers ($\log_{10} IU/ml, P = 0.018$).

CA noncarriers of A*03 had the highest rates of viral decline compared to CA carriers; the estimated mean viral level declines for the first 4 weeks were: 2.65 for CA noncarriers, 1.49 for AA noncarriers, 0.94 for CA carriers, and 1.21 for AA carriers ($\log_{10} IU/ml, P = 0.018$).

CA carriers of Cw*03 had the largest rates of viral decline compared to CA noncarriers, while AA noncarriers had higher rates of viral decline than did the AA carriers. The estimated mean viral level declines for the first 4 weeks were: 2.99 for CA carriers, 2.49 for CA noncarriers, 1.51 for AA noncarriers, and 1.19 for AA carriers ($\log_{10} IU/ml$, Fig. 2D). For all four of these alleles, the viral subgenotype (1a or 1b) did not have an impact on outcome ($P > 0.05$).

**DISCUSSION**

This study examines the effects of genetic diversity in the human MHC on the dynamics of viral decline in subjects treated with peginterferon for chronic HCV. We utilized data from a large, well-characterized cohort of AAAs and CAs with genotype 1 HCV infections who underwent a standard treatment protocol. We genotyped the A, B, and C class I loci, as well as the DRB1, DQA1, DQB1, DPA1, and DPB1 class II loci, and observed significant associations of two class I alleles and two class II alleles with the dynamics of the viral decline.

We also observed that the carriage of DQA1*04 or DQB1*0402 alleles was associated with slower rates of viral decline. Interestingly, the frequencies of these alleles are greater among AAAs than among CAs (Table 2). In addition, carriage of each of these alleles is associated with a greater difference in the level of viral decline among CAs than among AAAs. The frequency of DQA1*04 is 10.1% among AAAs and 2.8% among CAs; the frequency of DQB1*0402 is 8.1% among AAAs and 2.8% among CAs. Differential distribution of the frequencies of these alleles by race may contribute to the observed population differences in response to peginterferon by race on the population level.

The DQA1*04 and DQB1*04 alleles have been previously implicated as a risk for Crohn’s disease (31) and cirrhosis (10) in chronic HCV infections. The DQB1*0401/*0402 alleles are associated with viral persistence in several Japanese studies (1, 10, 15, 23). Previous studies that have examined the structure of DQB1*04 have shown that a leucine substitution exists at position 56 (21), which is located in the antigen-binding groove of the DQ molecule and probably contributes to the ability to present HCV peptides. The leucine substitution is present only in the DQB1*0401 and DQB1*0402 alleles. All other DQB1 alleles have a proline at this position. Future studies are needed to specifically examine HCV antigen presentation in the context of these two class II MHC alleles.

In addition, the DQB1*0402 and DQA1*04 alleles exist as a haplotype and, therefore, our findings of similar magnitude...
and direction of effects for the individual alleles are not surprising. Because the DQA1*04 and DQB1*0402 alleles often exist on a haplotype with DRB1*08 or DRB1*03, we examined whether carriage of the DRB1*08-DQA1*04-DQB1*0402 or DRB1*03-DQA1*04-DQB1*0402 haplotypes was associated with viral dynamics. However, due to the relatively low frequency of individuals with DRB1*08-DQA1*04-DQB1*0402 (4 AA and 10 CA patients) and DRB1*03-DQA1*04-DQB1*0402 (24 AA and 0 CA patients) in the cohort overall and the extreme distributions within each race, we were not able to obtain meaningful results with our longitudinal analyses (data not shown) and, therefore, are not able to exclude the possibility that another allele in linkage disequilibrium with the DQA1*04 or DQB1*0402 may negatively affect viral decline during therapy. Extended haplotypes involving DQB1*0401/*0402 have also been associated with greater HCV-induced liver injury (15), although the immediate fundamental relevance with respect to viral dynamics is not clear.

CA noncarriers of the class I allele A*03 had greater rates of viral decline than CA carriers. In contrast, AA noncarriers had slower rates of viral decline than AA carriers (Fig. 2C), unlike the effect within CAs. The effects of allele carriage appear to be greater among CA noncarriers and carriers than among AA noncarriers and carriers. Overall, the frequency of the A*03 allele is slightly lower among AAs than CAs (11.2% among AAs and 14.2% among CAs). It is possible that the main effects of this allele are seen among CAs, and that the smaller differences in viral dynamics among AA noncarriers and carriers is due to other undetermined genetic and/or nongenetic factors. It is also possible that AA and CA haplotype differences may contribute to the observed differences. Alternatively, it is possible that our observations are due to chance. Larger studies are needed to evaluate the potential effects of extended haplotypes within each race.

Carriers of Cw*03 had more pronounced viral dynamic declines than CA noncarriers (Fig. 2D). Viral declines among AA carriers and noncarriers were similar. Class I alleles are important in CD8+ T cells responses, which have been shown to play a role in the clearance of HCV during therapy (28). Future studies are needed to understand the role of Cw*03 in HCV antigen presentation. Overall, the frequency of the Cw*03 allele is similar among AAs and CAs (10.9% among AAs and 10.3% among CAs).

In summary, our observations suggest that carriage of DQA1*04 and DQB1*0402, or another allele in linkage disequilibrium with these alleles, may represent a risk for slower rates of viral decline during peginterferon therapy. With both DQA1*04 and DQB1*0402, CA noncarriers had better rates of viral decline during the course of therapy compared to CA carriers, AA noncarriers, and AA carriers, respectively (Fig. 2C and D).

The 28-day viral response represents a critical biological point for the study of the response to therapy due to its prognostic potential (16, 17, 19). Unlike SVR, early viral responses are less likely to be affected by dose adjustments and patient compliance and may therefore represent a more purely biologic picture of the role of host genetics in the interferon response. It is likely that in a complex process such as the response to peginterferon treatment for chronic HCV infection, multiple genes are involved, with different genes possibly operating at different time points during the course of therapy. Therefore, it is possible that the alleles that we describe here play an important role, either independently, as a haplotype, or in combination with other unidentified genetic markers during

### Table 2. Distribution of MHC class I and class II alleles in the Virahep-C cohort

| Allele        | AA (%) | CA (%) |
|---------------|--------|--------|
| **Class I**   |        |        |
| A locus       |        |        |
| A*01          | 22 (6.1) | 55 (14.2) |
| A*07          | 57 (15.9) | 104 (26.8) |
| A*03*         | 40 (11.2) | 55 (14.2) |
| A*23          | 13 (3.6) | 44 (11.3) |
| A*24          | 34 (9.4) | 19 (4.9) |
| A*68          | 45 (12.6) | 5 (0.7) |
| **B locus**   |        |        |
| B*07          | 22 (6.1) | 58 (14.9) |
| B*08          | 18 (5.0) | 35 (9.0) |
| B*15          | 49 (13.7) | 22 (5.7) |
| B*35          | 24 (6.7) | 32 (8.7) |
| B*44          | 21 (5.9) | 54 (13.9) |
| B*53          | 40 (11.2) | 5 (1.3) |
| **C locus**   |        |        |
| C*03          | 39 (10.9) | 40 (10.3) |
| C*04          | 64 (17.9) | 42 (10.8) |
| C*06          | 28 (7.8) | 40 (10.3) |
| C*07          | 56 (15.6) | 110 (28.4) |
| C*12          | 9 (2.5) | 31 (8.0) |
| C*1601        | 41 (11.5) | 19 (4.9) |

| **Class II**  |        |        |
| **DRB1 locus**|        |        |
| DRB1*03       | 48 (13.4) | 42 (10.8) |
| DRB1*07       | 39 (11.2) | 56 (14.4) |
| DRB1*11       | 50 (14.0) | 24 (6.1) |
| DRB1*13       | 65 (18.2) | 52 (13.4) |
| DRB1*15/*16   | 17 (4.7) | 69 (17.8) |
| **DQA1 locus**|        |        |
| DQA1*01       | 51 (14.2) | 51 (13.1) |
| DQA1*01/02    | 103 (28.3) | 86 (22.2) |
| DQA1*01/03    | 22 (6.1) | 35 (9.0) |
| DQA1*02       | 43 (12.0) | 57 (14.7) |
| DQA1*03       | 38 (10.6) | 68 (17.5) |
| DQA1*04       | 36 (10.1) | 54 (14.2) |
| DQA1*05       | 65 (18.2) | 77 (19.8) |
| **DQB1 locus**|        |        |
| DQB1*02       | 64 (1.9) | 62 (16.0) |
| DQB1*02/01    | 47 (4.7) | 22 (5.7) |
| DQB1*03       | 54 (15.1) | 52 (13.4) |
| DQB1*03/02    | 43 (11.9) | 43 (11.1) |
| DQB1*04       | 29 (8.1) | 11 (2.8) |
| DQB1*05       | 52 (14.5) | 37 (9.5) |
| DQB1*06       | 65 (18.2) | 68 (17.5) |
| **DPB1 locus**|        |        |
| DPB1*01       | 83 (23.2) | 266 (68.6) |
| DPB1*01/03/06 | 36 (10.1) | 33 (8.5) |
| DPB1*02/01/03 | 83 (23.2) | 31 (8.0) |
| DPB1*02/01/03 | 36 (10.1) | 33 (8.5) |
| DPB1*02/02    | 39 (10.9) | 2 (0.5) |

**Note:** The table presents allele frequencies (2N). The numbers of alleles, as well as the corresponding percentages, are categorized by race. There were a total of 179 AA and 194 CA participants in the Virahep-C genetics study.
the early period after the start of therapy, while other markers may exert a more influential role at subsequent time points during the course of therapy. In the future, larger studies are needed to refine the potential influence of extended MHC haplotypes on HCV viral dynamics during treatment.

Previous mathematical models using differential equations have suggested that the shape of the viral decline with standard alpha interferon or peginterferon is nonlinear. For example, biphasic and triphasic declines have been reported (9, 22). However, these models are based on very frequent sampling of viral levels spaced only hours apart, as opposed to days apart as with our study, meaning that the frequency and spacing of viral level measurements are critical to the modeling of viral kinetics. In the absence of intensive sampling of viral levels, we used a square root transformation of the time scale to linearize the trajectory of the viral decline for our statistical modeling. This approach allowed us to focus our analysis on the linear relationship of MHC allele carriage and the trajectories of viral levels over time.

A key factor in genetic association studies is the potential for confounding from population stratification. We have previously utilized recently developed techniques in mathematical genetics to infer individual admixture and found self-reported race to be highly correlated with individual admixture. Consequently, we have utilized self-reported race in our study (30). In addition, due to the hypothesis-generating nature of the present study, we have deliberately elected to not adjust for the number of comparisons made rather than reject an association solely based on statistical grounds (29). Although it is possible that the associations that we have observed are false positives, the consistent patterns within each race provide additional evidence of potential biological effects (Fig. 2).

Our study offers an important first picture of the role of diversity in the human MHC on the dynamics of viral decline during the first 28 days of therapy. Future studies are needed to confirm our observations, as well as expand our understanding of the biological mechanisms of these alleles in the context of HCV therapy. We have previously reported that the A*02, B*58, and DPB1*1701 alleles are associated with the SVR to alpha peginterferon-plus-ribavirin therapy (25). The response to therapy is likely a complex process that occurs over the course of time. Most likely, different combinations of genes are involved at different time points to clear viremia. For example, studies of Caucasian populations have consistently shown that the class II alleles DRB1*11 and DQB1*0301 are associated with natural clearance of HCV viremia (11, 29). However, a clear understanding of the biological mechanisms of these alleles is still lacking. Additional research, particularly with understanding of the differences in the presentation of HCV peptides by different HLA alleles, is needed to better understand the differences that we have observed between early viral dynamics and SVR. Additional nongenetic factors, such as decreased immune function through coinfections, may also play a role. Further research is needed to help evaluate

| Effect type | FE parameterb | DQA1*04 FE (SE) | DQB1*0402 FE (SE) | A*03 FE (SE) | Cw*03 FE (SE) |
|-------------|---------------|----------------|-------------------|--------------|---------------|
| On initial status | Intercept (γ_0) [estimated initial viral levelc] | 6.27 (0.146) | 6.28 (0.155) | 6.16 (0.100) | 6.14 (0.109) |
| | Allele (γ_a) [effect of noncarriage on initial status] | -0.08 (0.140) | 0.574 | 0.06 (0.1049) | 0.600 |
| | Race (γ_r) [effect of AA on initial status] | -0.03 (0.090) | 0.756 | -0.02 (0.089) | 0.855 |
| On rate of change | Time (γ_t) [estimated avg rate of changec] | -0.47 (0.248) | <.001 | -1.05 (0.1112) | <.0001 |
| | Allele-by-time (γ_{at}) [effect of noncarriage on the rate] | -0.86 (0.255) | <.001 | -0.33 (0.1288) | 0.309 |
| | Racc-by-time (γ_{rt}) [effect of AA on the rate] | -0.13 (0.282) | 0.129 | 0.23 (0.168) | <.0001 |
| | Allele-by-race-by-time (γ_{atr}) [effect of AA-by-noncarriage on the rate] | 0.70 (0.295) | 0.018 | 0.46 (0.192) | 0.018 |

FE, fixed effects. Viral levels below the lower limit of detection for the assay (600 IU/ml) were imputed using uniform distribution. Note that time was expressed as weeks in our actual calculations. A square root transformation was also applied to the time variable to ensure linearity.

See the supplemental material for interpretation of these parameters. * For the CA and carrier group. Viral levels were log10 transformed to approximate a normal distribution. A description for each model is given in brackets.

Statistically significant values are indicated in boldface.
these factors, as well as the functional characteristics of these alleles on HCV elimination.

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FIG. 2. The predicted mean decline of HCV viral levels by allele carriage and race. The vertical axis presents log_{10} transformed predicted mean viral levels from the random coefficients model, while the horizontal axis presents time. The time variable was expressed as days. In addition, predicted baseline viral levels along with the rates of viral change, are provided below each figure by race and the carriage of each of the alleles over time (with a /\sqrt{\text{week}} transformation). (A) DQA1^04; (B) DQB1^0402; (C) A^03; (D) Cw^03.
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