Published in final edited form as:
Genes Immun. 2008 June ; 9(4): 328–333. doi:10.1038/gene.2008.21.

Associations between the human MHC and sustained virologic response in the treatment of chronic hepatitis C virus infection

SL Rhodes[1], **H Erlich**[2], **KA Im**[3,4], **J Wang**[2], **J Li**[2], **T Bugawan**[2], **L Jeffers**[5], **X Tong**[1], **X Su**[1], **HR Rosen**[6], **LJ Yee**[4,7], **TJ Liang**[8], and **H Yang**[1,9] **for the Virahep-C Study Group**

1 *Cedars Sinai Medical Center, Los Angeles, CA, USA*

2 *Roche Molecular Systems, Inc., Alameda, CA, USA*

3 *Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA*

4 *Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA*

5 *Department of Medicine, Center for Liver Diseases, Veterans Affairs Medical Center, Miami, FL, USA*

6 *Division of Gastroenterology and Hepatology, University of Colorado Health Sciences Center, Denver, CO, USA*

7 *Division of Infectious Diseases, Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA*

8 *Liver Diseases Branch, NIDDK, National Institutes of Health, Bethesda, MD, USA*

9 *Department of Discovery, Medicine and Epidemiology, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA*

Abstract

The human major histocompatability complex (MHC) genes encode the human leukocyte antigens, which are important in antigen presentation and regulation of CD8 + and CD4 + T cells. Response to therapies in hepatitis C virus (HCV) infection is highly variable (30–80%) and lower response rates have been reported among African Americans (AA; ~30%) compared to Caucasian Americans (CA; ~50%) infected with genotype-1 viruses. We evaluated whether MHC gene variants were associated with response to therapy and racial differences in AA and CA sustained virologic response (SVR) rates. We genotyped alleles at 8 MHC loci: 3 class I (A, B and C) and 5 class II (DRB1, DQA1, DQB1, DPA1 and DPB1) loci in 373 individuals (179 AA and 194 CA) with genotype-1 HCV infections, who were treated with peginterferon-α-2a and ribavirin. We observed carriage of A*02 (RR = 1.33(1.08–1.64); P = 0.008), B *58 (RR = 1.84(1.24–2.73); P = 0.002) and DPB1*1701 (RR = 1.57(1.09–2.26); P = 0.015) to be associated with SVR after adjustment for other predictors of response. In analysis of AA and CA subgroups separately, we observed potential, though not statistically significant, differences in these MHC associations. Variation in the immunogenetic background of HCV-infected individuals might account for some observed variation in viral-specific immunity and courses of disease. In this regard, future studies examining broader patient populations are warranted.

Correspondence: Dr LJ Yee, University of Pittsburgh, A511 Crabtree Hall, 130 DeSoto Street, Pittsburgh, PA 15261, USA. E-mail: E-mail: YeeL@edc.pitt.edu.

Supplementary Information accompanies the paper on Genes and Immunity website (http://www.nature.com/gene)

Keywords

human major histocompatability complex; chronic hepatitis C infection; pegylated interferon and ribavirin therapy; African Americans; Caucasian Americans

Introduction

Within the United States approximately 20–30% of people infected with the hepatitis C virus (HCV) appear to mount an adequate immune response to clear the virus without therapeutic intervention;[1,2] the remaining 70–80% of patients become chronically infected. Currently, therapy for chronic HCV infection consists of pegylated interferon-α in combination with the nucleoside analog, ribavirin, given for 24 or 48 weeks and is effective in eliminating virus from 30–80% of those treated.[3,4] However, successful clearance of the virus with therapy can depend upon many factors including viral factors such as viral genotype and viral load at the start of treatment, and host factors including patient age, gender and the presence of co-morbidities such extensive fibrosis or cirrhosis and hepatic steatosis.[3,5] The race to which the patient belongs appears to strongly influence the response to therapy. We and others have reported African Americans (AAs) having significantly lower response rates to combination pegylated interferon (peginterferon) and ribavirin therapy compared to Caucasian Americans (CAs).[5–7] This racial difference and the broad spectrum of response to therapy suggest a possible role for host genetic diversity in the response to anti-HCV therapy.

Genes encoding the human leukocyte antigens (HLA) are found in the human major histocompatability complex (MHC) region of chromosome 6, and are critical in the regulation and initiation of the cellular immune response. MHC class I and class II molecules present foreign antigens to T-cell receptors bearing CD8 + and CD4 + T-lymphocytes, respectively. Interferon-α has been identified as an immunomodulatory cytokine that induces T-lymphocyte activation and expression of MHC molecules. Numerous class I and class II HLA polymorphisms appear to be related to spontaneous clearance in studies comparing self-limiting and chronic HCV infection.[8] The reports by studies investigating MHC polymorphisms and response to interferon-based therapy have been largely inconsistent, and the studies themselves are characterized by considerable heterogeneity arising from factors such as differences in ethnic composition, genes evaluated and genotyping method. We examined whether specific MHC alleles are associated with the sustained virologic response (SVR) to peginterferon-ribavirin therapy for chronic, genotype-1 HCV infection in the Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C) cohort.

Results

Cohort characteristics

Among the 401 individuals who were treated in the Virahep-C Study,[5] 373 consented to participate in host genetics studies and had DNA available for genotyping. Forty-nine (27.4%) of AA subjects and 104 (53.6%) of CA subjects were classified as sustained virologic responders. Table 1 summarizes the baseline characteristics of the participants contributing to this analysis. Statistically significant differences were detected in gender, fibrosis score, viral level at baseline and amount of peginterferon dosage taken. The observed percent SVR was higher for females, patients with lower fibrosis scores, patients with lower baseline viral levels (≤ 6.5 $\log_{10}$ IU ml^{-1}) and participants who took greater than 96% of the peginterferon dosage provided.

Carrier frequency analysis

In our study sample, we observed 12 alleles at the MHC A locus, 11 alleles at the B locus and 11 alleles at the C locus, within the class I region with carrier frequencies ≥5%. We observed 10, 7, 8, 8 and 6 alleles at the DRB1, DQA1, DQB1, DPA1 and DPB1 loci, respectively, within the class II region ≥5%. Table 2 presents the race-adjusted Mantel–Haenszel χ^2 test results for the four alleles with a race-adjusted *P*-value less than or equal to 0.05; results for all alleles evaluated by Mantel–Haenszel χ^2 tests are listed in Supplementary Tables 1 and 2 (available at the Genes and Immunity web site). The class I allele A*02 was found in 30% of AA and 46% of CA. Of AAs carrying the A*02 allele, 33% achieved SVR whereas 25% of the AA non-carriers achieved SVR. Of the CAs carrying the A*02 allele, 64% achieved SVR compared to 46% of CA non-carriers. We observed similar trends for the B*58 and DPB1*1701 alleles, although these alleles are uncommon in our CA sample (1 and 3%, respectively). Fourteen percent of our AA sample were carriers of the B*58 allele, and of these carriers 48% achieved SVR compared to 24% of non-carriers. The DPB1*1701 allele was identified in 15% of AA participants, of whom 42% achieved SVR compared to 25% of the non-carriers. DPA1*0103 was found in 30% of AAs and 75% of CAs in our study. Of the AAs carrying the DPA1*0103 allele 15% achieved SVR compared to 33% of the AA non-carriers. Of the CAs carrying the DPA1*0103 allele 52% achieved SVR compared to 58% of CA non-carriers.

Regression analysis

Table 3 summarizes the relative risk (RR) estimates for carriage of each of the four alleles with *P*-values less than 0.05 in the carrier frequency analysis. Regression results and RR estimates for all alleles with *P*-values less than 0.15 in carrier frequency analysis are presented in Supplementary Table 3 (available at the Genes and Immunity web site). In single allele regression models that included other predictors of response to therapy, three alleles remained significantly associated with SVR: A*02, B*58 and DPB1*1701. Table 4 presents the RR estimates for a regression model that includes demographic, clinical and virologic predictors of response, as well as the three HLA alleles, A*02, B*58 and DPB1*1701. In analysis of the combined AA and CA study sample, all three alleles remained independently associated with SVR after adjustment for each other and other predictors of response. Evaluation of this regression model in the AA and CA subgroups separately differed slightly from the results of the combined sample (Table 4).

Discussion

The major histocompatibility loci that encode the HLA class I and II molecules, which recognize and bind T-cell epitopes in viral proteins, represent among the most highly polymorphic genes in the human population. In this cohort study of genetically diverse patients with chronic HCV infection, we observed that the A*02, B*58 and DPB1*1701 HLA alleles were independently associated with SVR even after adjustment for other predictors of response such as race, gender, baseline viral load, severity of liver fibrosis and dosage of medication taken. While these alleles do not explain all of the observed racial differences in response to peginterferon-ribavirin therapy, they might be contributing factors that work in conjunction with other factors to affect differences in response.

We note that A*02 is positively associated with SVR ($P = 0.008$, Table 3) in both CA and AA samples and is more frequent among CA patients (46% carrier frequency) than among AA patients (30%). Conceivably, this difference in A*02 frequency between the two ethnic groups might account, in part, for the increased SVR rate among Caucasian patients. The other highly significant association in this data set with SVR is for B*58 ($P = 0.002$, Table 3). This allele is found more frequently among AA patients (14% carrier frequency) than among CA patients (1%). However, as B*58 is much less frequent among AA patients than A*02 is among CA

patients, this allele may have less effect on the relative SVR rates of the two populations than does A*02.

In the regression model containing all alleles with other predictors of response (Table 4), we observed different levels of significance for those alleles in the AA and CA subgroups compared to each other and compared to the combined sample. These subgroup evaluations should be interpreted with caution as both subgroups contain fewer than 200 subjects (AA *n* = 179 and CA *n* = 194), some allele frequencies were very low in certain subgroups (Table 3), and, particularly for the AA subgroup, the number of subjects achieving SVR is small; thereby contributing to the wider confidence intervals and lack of statistical significance observed in the subgroup analyses. Nevertheless, the RR estimates (Table 4) within the subgroups and in the combined sample were in the same direction for all alleles and, for A*02, of a similar magnitude. For B*58 and DPB1*1701, the RR estimates in the AA subgroup were larger than those in the CA subgroup indicating a possible heterogeneity of effect between our AA and CA study samples for these alleles or others in strong LD (linkage disequilibrium) with B*58 or DPB1*1701.

None of these three alleles have previously been reported in association with response to peginterferon plus ribavirin therapy for HCV infection. The A*02 antigen was reported in association with lower alanine transaminase levels in chronically HCV-infected Japanese subjects.[9] The A*02-B*27-Cw*01 haplotype was found in strong LD with the DRB1*0101-DQB1*0501 haplotype, which was associated with HCV clearance in an Irish population, as were the B*27 and Cw*01 alleles alone.[10] This could indicate that one or more loci in LD with A*02 are influencing immune response to hepatitis C infection. In our sample, two subjects (1 AA and 1 CA) carried both A*02 and B*58, four subjects (2 AA and 2 CA) carried both A*02 and DPB1*1701, five subjects (all AAs) carried both B*58 and DPB1*1701, and no subjects carried all three alleles, therefore, we did not investigate haplotype associations in this cohort.

The A*02 allele has been reported in association with other infectious diseases and/or complications. In particular, in Japanese subjects infected with human T-cell lymphotropic virus type I (HTLV-I), the A*02 allele was associated with protection from HTLV-I-associated myelopathy, and in healthy carriers of HTLV-I, the A*02 allele was associated with lower viral load.[11] The A*02-Cw16 haplotype was associated with high viral load in HIV-1, clade C-infected Zambians.[12] Finally, a study of C282Y homozygous hemochromatosis subjects demonstrated a significant association between the A*02 allele and a lower CD8+ T-lymphocyte count.[13] This association was not observed in healthy controls carrying the A*02 allele, indicating that the lower count may be related to a locus in LD with the A*02 allele. We identified one published report[14] of an association between the B*5802 allele and higher viral load in HIV-1 subtype C-infected Zambians, although the B*5801-Cw*03 haplotype was associated with lower viral load. Furthermore, an association between the B*58 allele and higher T-cell response in vertically-HIV-infected AA children (predominately females) has been reported.[15]

Differences in the immunogenetic background of HCV-infected individuals might, in part, account for the observed variation in viral-specific immunity and courses of disease.[16] In this regard, binding of HCV peptides to HLA molecules is a critical step for the initiation of an antigen-specific immune response. Previous work from Virahep-C has indicated that baseline HCV-specific immunity is associated with SVR;[17] patients with higher levels of CD4 + T-cell responses are more likely to develop SVR than patients with lower pretreatment levels. Moreover, the frequency of circulating effector cytotoxic T-cell lymphocytes before treatment was also shown to predict SVR.[18] It is of considerable interest that the A*02 allele, the most common restricting allele for known HCV epitopes (http://www.hcv.lanl.gov), was strongly

associated with SVR in the current study. Thus, one might speculate that a patient carrying the HLA A*02 allele would have a considerably greater likelihood of having T cells that recognize HCV peptides displayed on infected hepatocytes compared to patients not carrying this allele. This relatively augmented immune background might lead to HCV that is more susceptible to the antiviral pressure induced by therapy. The relative rarity of HLA B*58 limits its clinical utility as a predictor of response; notably, no known HCV epitopes restricted by this allele have been reported (http://www.hcv.lanl.gov). On the other hand, it is conceivable that HLA genotyping for A*02 might provide additional prognostic information for patients with chronic HCV undergoing antiviral therapy.

Our study involved a select group of patients undergoing a standardized treatment protocol.[5] Participants had to meet specific selection criteria: all had mild fibrosis, were interferon-treatment naïve and were infected with genotype-1 HCV. Future studies examining a broader patient population are warranted. Additionally, our study employed medium resolution typing of the MHC region; studies of higher resolution typing might further inform the relationship between MHC alleles and SVR in the treatment of hepatitis C. Studies are also needed to understand the function of HLA molecules and how they present HCV antigens. Moreover, the elimination of HCV during therapy is a dynamic process that occurs over the course of time. It is possible that alleles capable of presenting a broad range of HCV antigens are needed at certain time points during the elimination of the virus, while other alleles, more specific with respect to the HCV antigens that they present, are needed at other time points. Future studies should identify whether alleles with different HCV antigen-presenting characteristics are needed at different time points during the course of therapy. In conclusion, we observed that certain MHC gene variants were associated with SVR to peginterferon-ribavirin therapy. These MHC associations by themselves, however, are insufficient to account for the observed differences in AA and CA response rates even though there are large differences between AA and CA allele frequencies for the associated variants. Thus, our data suggest that one or more additional genetic factors contribute to the racial difference in response. Confirmation of these results in other AA and CA populations, as well as in other racial or ethnic groups, will be necessary to further understand the role of MHC genes in an individual's response to HCV therapy and the degree of genetic contribution to that response.

Methods

Study population

Subjects included in this analysis were participants in the Virahep-C Study, a multi-center study sponsored by the National Institutes of Health aimed at understanding the mechanisms of resistance to antiviral therapy for chronic HCV infection among interferon treatmenaaïve individuals infected with genotype-1 (1a and 1b) HCV, as well as the differences in outcome by race among AAs and CAs. Details of this study have been published previously.[5] All subjects were born in the United States and race was determined by a self-administered questionnaire.

Virologic assessment

Quantitative measurements of viral levels were obtained using the Roche Amplicor assay version 2 at baseline, during treatment, at the end of treatment (24 weeks) and at the end of follow-up (48 weeks following the start of treatment). SVR was defined as undetectable HCV RNA (<50 IU ml^{-1}) 24 weeks following end of treatment; subjects who did not achieve this level of viral load were considered non-responders.

MHC genotyping

We genotyped the three class I genes and the five most highly polymorphic class II genes. Genotyping of the class I loci (A, B and C), along with the class II loci (DRB1, DQA1, DQB1, DPA1 and DPB1) was conducted using medium resolution genotyping methods developed by Roche Molecular Systems,[19,20] which use sequence-specific oligonucleotide probes immobilized on nylon membranes and uses the Profiblot semiautomated hybridization system. All typing of MHC genes was conducted by Roche Molecular Systems (Alameda, CA, USA).

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[21] and utilized the structured association method developed by Pritchard and colleagues to evaluate the population structure.[22,23] We have previously observed a strong correlation between self-reported race and individual admixture in this study sample.[21] We obtained similar results under both models during our analyses using individual estimates of admixture and using self-reported race. Consequently, we present the results of self-reported race.

Data analyses

For all alleles with a carrier frequency greater than 5% in the combined sample or in either racial subgroup, we evaluated the carrier status for association with SVR within each racial subgroup using a χ^2 statistic and in the combined sample using a race-adjusted Mantel–Haenzel RR estimate. All alleles with a *P*-value less than 0.15 in the race-adjusted carrier test were evaluated, individually, in a multivariable Poisson regression model[24] with other factors that we have previously identified to be associated with SVR in this study population (race, gender, $\log_{10}$ baseline viral load, baseline viral load by race interaction term, Ishak fibrosis score and percentage of peginterferon dosage received in the first 24 weeks).[5] Alleles that remained significant ($P \leq 0.05$) in the single allele regression were placed in a Poisson regression model[24] together, again with other predictors of response. This model was evaluated for the combined sample and for AA and CA subgroups separately.

Acknowledgments

This clinical study was a cooperative agreement funded by the NIDDK and co-funded by the National Center on Minority Health and Health Disparities (NCMHD), with a Cooperative Research and Development Agreement (CRADA) with Roche Laboratories, Inc. Grant numbers: U01 DK60329, U01 DK60340, U01 DK60324, U01 DK60344, U01 DK60327, U01 DK60335, U01 DK60352, U01 DK60342, U01 DK60345, U01 DK60309, U01 DK60346, U01 DK60349 and U01 DK60341. Other support: National Center for Research Resources (NCRR), NIDDK Intramural Program (TJL), National Cancer Institute, Center for Cancer Research, General Clinical Research Centers Program Grants: M01 RR00645 (New York Presbyterian), M02 RR000079 (University of California, San Francisco), M01 RR16500 (University of Maryland), M01 RR000042 (University of Michigan) and M01 RR00046 (University of North Carolina). Additional support for Dr Leland J Yee was provided by a National Institutes of Health Clinical Research Career Development Award Grant 1KL2 RR024154-02.

References

1. Alter MJ. Hepatitis C virus infection in the United States. J Hepatol 1999;31 (Suppl 1):88–91. [PubMed: 10622567]
2. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–714. [PubMed: 16702586]
3. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–982. [PubMed: 12324553]

4. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–965. [PubMed: 11583749]
5. Conjeevaram HS, Fried MW, Jeffers LJ, Terrault NA, Wiley-Lucas TE, Afdhal N, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. Gastroenterology 2006;131:470–477. [PubMed: 16890601]
6. Howell CD, Jeffers LS, Cassidy W, Reddy KR, Hu S, Lee JS. Peginterferon alfa-2a and ribavirin for chronic hepatitis C genotype 1 infections in black patients: safety, tolerability and impact on sustained virologic response. J Viral Hepat 2006;13:371–376. [PubMed: 16842439]
7. Jeffers LJ, Cassidy W, Howell CD, Hu S, Reddy KR. Peginterferon alfa-2a (40 kd) and ribavirin for black American patients with chronic HCV genotype 1. Hepatology 2004;39:1702–1708. [PubMed: 15185312]
8. Singh R, Kaul R, Kaul A, Khan K. A comparative review of HLA associations with hepatitis B and C viral infections across global populations. World J Gastroenterol 2007;13:1770–1787. [PubMed: 17465466]
9. Kondo Y, Kobayashi K, Kobayashi T, Shiina M, Ueno Y, Satoh T, et al. Distribution of the HLA class I allele in chronic hepatitis C and its association with serum ALT level in chronic hepatitis C. Tohoku J Exp Med 2003;201:109–117. [PubMed: 14626512]
10. McKiernan SM, Hagan R, Curry M, McDonald GS, Kelly A, Nolan N, et al. Distinct MHC class I and II alleles are associated with hepatitis C viral clearance, originating from a single source. Hepatology 2004;40:108–114. [PubMed: 15239092]
11. Jeffery KJ, Siddiqui AA, Bunce M, Lloyd AL, Vine AM, Witkover AD, et al. The influence of HLA class I alleles and heterozygosity on the outcome of human T cell lymphotropic virus type I infection. J Immunol 2000;165:7278–7284. [PubMed: 11120862]
12. Tang J, Tang S, Lobashevsky E, Myracle AD, Fideli U, Aldrovandi G, et al. Favorable and unfavorable HLA class I alleles and haplotypes in Zambians predominantly infected with clade C human immunodeficiency virus type 1. J Virol 2002;76:8276–8284. [PubMed: 12134033]
13. Cruz E, Vieira J, Almeida S, Lacerda R, Gartner A, Cardoso CS, et al. A study of 82 extended HLA haplotypes in HFE-C282Y homozygous hemochromatosis subjects: relationship to the genetic control of CD8+ T-lymphocyte numbers and severity of iron overload. BMC Med Genet 2006;7:16. [PubMed: 16509978]
14. Lazaryan A, Lobashevsky E, Mulenga J, Karita E, Allen S, Tang J, et al. Human leukocyte antigen B58 supertype and human immunodeficiency virus type 1 infection in native Africans. J Virol 2006;80:6056–6060. [PubMed: 16731944]
15. Sharp ER, Barbour JD, Karlsson RK, Jordan KA, Sandberg JK, Wiznia A, et al. Higher frequency of HIV-1-specific T cell immune responses in African American children vertically infected with HIV-1. J Infect Dis 2005;192:1772–1780. [PubMed: 16235176]
16. Zavaglia C, Martinetti M, Silini E, Bottelli R, Daielli C, Asti M, et al. Association between HLA class II alleles and protection from or susceptibility to chronic hepatitis C. J Hepatol 1998;28:1–7. [PubMed: 9537846]
17. Rosen HR, Weston SJ, Im K, Yang H, Burton JR Jr, Erlich H, et al. Selective decrease in hepatitis C virus-specific immunity among African Americans and outcome of antiviral therapy. Hepatology 2007;46:350–358. [PubMed: 17659573]
18. Golden-Mason L, Klarquist J, Wahed AS, Rosen HR. PD-1 expressin is increased on immunocytes in chronic HCV and predicts failure of response to antiviral therapy: race-dependent differences. J Immunol 2008;180:3637–3641. [PubMed: 18322167]
19. Mack, SJ.; Jani, AJ.; Geyer, LN.; Erlich, HA. Using the reverse line strip system for studies of human diversity. 13th IHWS Technology Joint Report. In: Hansen, JA., editor. Immunobiology of the Human MHC: Proceedings of the 13th International Histocompatibility Workshop and Conference; Seattle, WA: IHWG Press; 2007. p. 291-294.
20. Mack S, Sanchez-Mazas A, Single R, Meyer D, Hill J, Dron H, et al. Population samples and genotyping technology. Tissue Antigens 2007;69:188–191. [PubMed: 17445198]

21. Yee LJ, Tang YM, Kleiner DE, Wang D, Im K, Wahed A, et al. Myxovirus-1 and protein kinase haplotypes and fibrosis in chronic hepatitis C virus. Hepatology 2007;46:74–83. [PubMed: 17526009]

22. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. Genetics 2000a;155:945–959. [PubMed: 10835412]

23. Pritchard JK, Stephens M, Rosenberg NA, Donnelly P. Association mapping in structured populations. Am J Hum Genet 2000b;67:170–181. [PubMed: 10827107]

24. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702–706. [PubMed: 15033648]

Table 1

Subject characteristics

Factor	AA (n = 179)		CA (n = 194)		MH-race adjusted P-value[a]
	n	%SVR	n	%SVR	
Gender					
Male	117	23.9	126	48.4	0.016
Female	62	33.9	68	63.2	
Fibrosis score					
0	18	50.0	21	66.7	0.0023
1,2	96	26.0	96	57.3	
3,4	54	24.0	58	51.7	
5,6	10	20.0	19	26.3	
Baseline viral level (log10 IU ml^{-1})					
≤6.5	102	33.3	90	60.0	0.0095
>6.5	77	19.5	104	48.1	
Proportion of peginterferon dose taken in first 24 weeks[b]					
>0.96	76	33.5	105	66.7	<0.0001
≤0.96	97	21.7	88	38.6	

Abbreviations: AA, African American; CA, Caucasian American; IU, international units; MH, Mantel–Haenszel; SVR, sustained virologic response.

[a] Each *P*-value is the result of a stratified analysis using a Cochran–Mantel–Haenszel test, which evaluates an association between SVR and a given explanatory factor (for example, gender) after taking into account the racial difference in SVR.

[b] Proportion of peginterferon dose taken was not calculated for seven subjects due to incomplete data.

Table 2

Selected[a] MHC class I and class II allele carriers and sustained virologic response

Allele	AA		CA		MH-race adjusted	
	n	%SVR	n	%SVR	RR[b] (95% CI)	P-value[c]
A*02 carrier	54	33.3	88	64.4	1.38 (1.09, 1.74)	0.008
A*02 non-carrier	125	24.8	103	45.6		
B*58 carrier	25	48.0	2	100	1.98 (1.31, 2.99)	0.006
B*58 non-carrier	154	24.0	189	53.4		
DPB1*1701 carrier	26	42.3	5	80.0	1.64 (1.11, 2.43)	0.029
DPB1*1701 non-carrier	153	24.8	188	53.2		
DPA1*0103 carrier	54	14.8	145	52.4	0.73 (0.55, 0.97)	0.028
DPA1*0103 non-carrier	125	32.8	48	58.3		

Abbreviations: AA, African American; CA, Caucasian American; CI, confidence interval; MH, Mantel–Haenszel; RR, relative risk; SVR, sustained virologic response.

[a] Only alleles with a *P*-value less than or equal to 0.05 in MH-race adjusted χ^2 test are listed. Carrier frequency test results for all alleles tested are in Supplementary Tables 1 and 2 (available at the Genes and Immunity web site).

[b] Relative risk is estimating the risk of a carrier, compared with a non-carrier, achieving sustained response.

[c] *P*-values are not adjusted for multiple testing.

Table 3

Multivariable Poisson regression results modeling sustained virologic response by other predictors of response[a] and carrier status of the allele indicated

Allele	% of allele carriers in total sample		RR (95%CI)	P-value[b]
	AA	CA		
A*02	30	46	1.33 (1.08–1.64)	0.008
B*58	14	1	1.84 (1.24–2.73)	0.002
DPB1*1701	15	3	1.57 (1.09–2.26)	0.015
DPA1*0103	30	75	0.81 (0.64–1.02)	0.069

Abbreviations: AA, African American; CA, Caucasian American; CI, confidence interval; RR, relative risk.

[a] Other predictors of response include: race, gender, $\log_{10}$ baseline viral load, baseline viral load by race interaction term, Ishak fibrosis score and proportion of peginterferon dosage taken in the first 24 weeks. Relative risk estimates for these covariates are present in Supplementary Table 3 (available at the Genes and Immunity web site).

[b] *P*-values are not adjusted for multiple testing.

Table 4

Multivariable Poisson regression results modeling sustained virologic response by other predictors of response, A*02, B*58 and DPB1*1701 alleles carrier status

	Combined sample			AA sample		CA sample	
	RR	**95% CI**	**P-value[a]**	**RR**	**95% CI**	**RR**	**95% CI**
Race (CA)	2.22	1.63–3.04	<0.0001	NC		NC	
Gender (male)	0.76	0.61–0.93	0.0096	0.80	0.50–1.28	0.74	0.59–0.94
Baseline VL (log_{10})	0.59	0.45–0.77	<0.0001	0.59	0.44–0.78	0.86	0.75–0.98
Baseline VL*race (CA)	1.47	1.09–1.98	0.0112	NC		NC	
Ishak fibrosis score	0.90	0.83–0.97	0.0044	0.87	0.74–1.03	0.90	0.84–0.98
Dose received[b]	1.42	1.19–1.68	<0.0001	1.44	1.18–1.78	1.42	1.11–1.81
Carrier of A*02	1.30	1.05–1.60	0.0155	1.41	0.90–2.22	1.31	1.03–1.65
Carrier of B*58	1.74	1.17–2.60	0.0068	1.95	1.17–3.24	1.15	0.85–1.56
Carrier of DPB*1701	1.46	1.02–2.10	0.0410	1.70	0.97–2.96	1.13	0.79–1.61

Abbreviations: AA, African American; CA, Caucasian American; CI, confidence interval; NC, not calculated; RR, relative risk; VL, viral load.

[a] *P*-values are not adjusted for multiple testing.

[b] Proportion of peginterferon dosage taken in the first 24 weeks.