HAVCR1 Gene Haplotypes and Infection by Different Viral Hepatitis C Virus Genotypes

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The hepatitis A virus cellular receptor 1 (HAVCR1) gene is highly polymorphic, and several variants have been associated with susceptibility to allergic and autoimmune diseases. The HAVCR1 gene region was identified as a candidate for hepatitis C virus (HCV) natural clearance in a genotyping study of selected immune response genes in both European-American and African-American populations. The aim of the present study was to explore the influence of HAVCR1 in the outcome of HCV infection in the Spanish population. Three cohorts, consisting of 354 subjects with persistent HCV infection (285 with persistent HCV monoinfection and 69 with natural clearance), 182 coinfected HIV/HCV patients, and 320 controls, were included. Samples were genotyped in several polymorphic positions, insertion/deletion variants in exon 4 and tag single nucleotide polymorphisms (SNPs), in order to define previously described HAVCR1 haplotypes (haplotypes A to D). No statistically significant differences were observed with spontaneous resolution of infection or with viral clearance after treatment. Nevertheless, different rates of infection by viral genotypes (G’s) were observed among the HAVCR1 haplotypes. Individuals bearing haplotype C had the highest viral G1 infection rate when compared to individuals bearing other haplotypes (75.82% versus 57.72%, respectively; corrected P value [Pc], 3.2 × 10⁻⁴; odds ratio [OR], 2.30; 95% confidence interval [CI], 1.51 to 3.47). Thus, HAVCR1 could be involved in susceptibility or resistance to infection by a particular HCV genotype.

Hepatitis C virus (HCV) infection is estimated to affect 170 million people worldwide and remains a major cause of chronic liver disease (24). HCV is a small, enveloped, positive-strand RNA virus that has been classified in a separate genus (Hepacivirus) of the Flaviviridae family. An important feature of the HCV genome is its high degree of genetic variability; 6 major virus genotypes and about 100 subtypes, which often have distinct geographic distributions, have been identified (20). HCV infection results in chronic active hepatitis in more than 80% of infected patients; 20 to 30% of these patients develop progressive fibrosis and cirrhosis, whereas only approximately 10 to 20% of the infected people spontaneously eliminate the virus (24). The factors required for the generation of this effective immune response are largely unknown, and different factors have been evaluated as predictors of the sustained response to treatment, with controversial results (9). Recently, the interleukin-28B (IL28B) gene was strongly associated with sustained virological response to treatment (6, 22, 23), with natural viral clearance (25), and with different rates of viral genotype infection (12, 16). A study reporting an analysis of 112 selected immune response gene identified 4 gene regions as candidates for HCV natural clearance or persistence in both African-American and European-American populations (17): the TNFSF18, TANK, HAVCR1, and IL18BP gene regions. One of these genes is the hepatitis A virus cellular receptor 1 (HAVCR1, or TIM-1) gene, a member of the HAVCR family of genes encoding type 1 transmembrane glycoproteins with a conserved structure, which includes the immunoglobulin domain and the mucin domain (3, 4, 8). HAVCR1 expression has been found on several cell types, such as Th2, mast, NKT, B lymphocytes, and tubular epithelial cells of kidney (4, 13). Some studies indicated that Tim-1 (the mouse ortholog of HAVCR1) can bind to other Tim-1 proteins (19) and to Tim-4 (14). Thus, Tim-1 homophilic interactions (Tim-1–Tim-1) have been found in crystallization studies (19), and others have reported interactions between Tim-1 and Tim-4 via phosphatidylserine in exosomes (15). Tim-1 has a costimulatory and immunomodulatory effect on T cell responses, since the use of anti-Tim-1 antibodies simultaneously with T cell receptor (TCR) stimulation greatly enhanced Th proliferation and Th2 cytokine production (26). Nevertheless, Tim-1 costimulation prevents allogeneic transplant tolerance by reducing Foxp3 expression while enhancing development of Th1 and Th17 responses (2). Moreover, administration of agonistic anti-Tim-1 monoclonal antibodies (MAbs) during the induction phase of experimental autoimmune encephalomyelitis (EAE) enhanced pathogenic Th1 and Th17 responses and increased the severity of EAE (28). Additionally, in vitro stimulation of activated B cells with anti-TIM-1 MAbs enhanced proliferation and Ig production (11, 27). The HAVCR1 gene is highly polymorphic in promoter regions as well as in coding regions, with single nucleotide polymorphisms (SNPs) and insertion/deletion (ins/del) variants located throughout the gene and, more specifically, in the exon 4 encoding the functional mucin domain. In a previous study, we reported the 4 most common HAVCR1 gene haplotypes in our population; one of them, haplotype B, was associated with...
higher mRNA expression levels and susceptibility to rheumatoid arthritis (5). Because of the high degree of variability of this gene, it is possible that the variants associated with HCV infection depend on the population studied. The aims of the present study were, first, to replicate the association of the HAVCR1 gene with the natural clearance of HCV infection in the Spanish population and, second, to explore the influence of this gene in the outcome of HCV infection, taking into account the haplotypes described in our population.

MATERIALS AND METHODS

Subjects. Three cohorts of subjects were included in the study. Cohort 1 consisted of 285 subjects with persistent HCV infection (chronic hepatitis C [CHC]) (168 males and 117 females), including 69 individuals who naturally cleared the virus (29 males and 40 females), as described elsewhere (16). Briefly, data of responses to treatment (51.4% received alpha interferon [IFN-α], and 48.6% received IFN-α plus ribavirin [RBV]) were available in 219 patients; of these patients, 113 had a sustained response (SR) (HCV RNA levels remained undetectable for 6 months after therapy discontinuation) and 106 had a nonsustained response (NSR), including nonresponder patients (HCV RNA levels detectable during treatment) and relapsed responder patients (HCV RNA levels undetectable during therapy but detectable after discontinuation). With regard to the viral genotypes, 213 of the CHC patients were infected with viral genotype 1 (G1), 11 with viral genotype 2 (G2), 43 with genotype 3 (G3), and 11 with genotype 4 (G4), and the rest had coinfections with different HCV genotypes. Cohort 2 consisted of 182 coinfected HIV/HCV patients (153 males and 29 females), as described elsewhere (7). Data of responses to treatment (IFN-α plus RBV) were available in 126 patients; 68 of these patients had an SR, and 58 had an NSR. With regard to the viral genotypes, 87 were infected with viral G1, 2 with G2, 65 with G3, and 28 with G4. Cohort 3, a group of 320 bone marrow donors (5), was considered representative of the “normal” frequencies of the polymorphisms studied in the Spanish population. The study was approved by all local ethical committees of the corresponding hospitals. Blood samples were obtained from subjects after they provided written informed consent. Genomic DNA was extracted from blood leukocytes using the QIAamp DNA minikit (Qiagen, Hilden, Germany) according to the manufacturer’s recommendations and stored at −20°C.

HAVCR1 genotyping. Genotyping of the SNP rs953569 was performed using TaqMan probe assays (TaqMan SNP genotyping assays; C_1453925_10) on a 7500 Fast real-time PCR system (Applied Biosystems, Foster City, CA) according to the manufacturer’s instructions. Genotyping of the rest of the polymorphic positions was performed as previously described (5) to define previously reported HAVCR1 haplotypes (5), taking into account the three insertion/deletion variants in exon 4 of the HAVCR1 gene—5383_5397ins/del (rs6149307), 5387_5389ins/delAAC, and 5509_5511ins/delCAA (rs13173581)—and five tag SNPs—rs2134230, rs2277025, rs6878732, rs13173581, and rs2279804. Haplotypes of each individual were inferred using Famhap software version 19.1 (http://iweb.meb.uni-bonn.de/famhap/).

Statistical analysis. Genotypic and allelic frequencies of the markers studied were obtained by direct counting. The chi-square test was performed to compare distributions. The P values were corrected by multiplying the number of comparisons (creating P values) by 5. P values below 0.05 were considered statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated according to the Woolf method. The software used was Statcalc (Epi Info 2002; Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

In a recently published study, the SNP rs953569 was found to be associated with natural clearance of HCV infection (17), and the first aim of the present study was to replicate this study in a Spanish population of HCV-infected patients. Genotypes were unequivocally assigned in all of the cases except for in two individuals infected by G1: one of these individuals was included in the cohort of monoinfected HCV patients (cohort 1), and the other was included in the coinfected HIV/HCV cohort (cohort 2). The study population in the control group (cohort 3) was found to be in the Hardy-Weinberg equilibrium (27.18% had genotype G1, 50.00% had genotype GT, and 22.82% had genotype TT). When comparing the distributions of the rs953569 genotypes, no statistically significant differences were found either between the natural clearance and chronic hepatitis C groups (cohort 1) or between the SR and NSR groups (cohorts 1 and 2) (Table 1). Nevertheless, a different distribution of the rs953569 genotypes was found by stratifying patients of cohort 1 according to their viral genotype (G1 versus non-G1) (P = 0.006 in a 2 × 3 contingency table). This different distribution was due to an overrepresentation of the TT genotype among non-G1-infected patients (38.47%) compared to its representation among G1-infected patients (19.34%), P = 0.003, OR = 2.60, 95% CI = 1.43 to 4.75) and in the control cohort (P = 0.012, OR = 2.11, 95% CI = 1.21 to 3.70).

Next, we constructed HAVCR1 gene haplotypes in our three cohorts, also including the rs953569 SNP. The rs953569G variant was found within the A and C haplotypes, whereas the rs953569T variant was included within the B and D haplotypes (Table 2). Table 3 displays the results obtained when patients were stratified according to their HAVCR1 haplotypes. Haplotypes were unequivocally assigned in all of the cases except for in 5 individuals in

| Table 1 Frequency of the rs953569 genotypes in the HAVCR1 gene in the three cohorts included in this studya |
|-----------------------------------------------|
| Cohort and characteristic | No. of people with indicated genotype (% of total no. of people) |
| Cohort 1 |  |
| Spontaneous viral clearance |  |
| Chronic hepatitis C | 19 (27.53) 36 (52.17) 14 (20.30) |
| Sustained response | 82 (28.97) 133 (46.99) 68 (24.04) NS |
| Nonresponse | 35 (30.97) 53 (46.90) 25 (22.13) |
| Cohort 2 |  |
| Sustained response | 20 (29.41) 35 (51.47) 13 (19.12) |
| Nonsustained response | 17 (28.82) 29 (50.88) 19 (30.30) NS |
| Cohort 3 |  |
| Control | 87 (27.18) 160 (50.00) 73 (22.82) |

a Data of patients were stratified and compared according to whether the patients had spontaneous viral clearance or persistent infection, whether they had a sustained response or a nonsustained response, and whether they were infected with G1 or non-G1.

b 2 × 3 contingency table. NS, not significant.

c The TT genotype is overrepresented (versus the GG and GT genotypes) in non-G1-infected people when compared to its representation in G1-infected people (P = 0.003, OR = 2.60, 95% CI = 1.43 to 4.75) and in the control cohort (P = 0.012, OR = 2.11, 95% CI = 1.21 to 3.70).
cohort 1 with persistent infection (4 with viral G1 and 1 with viral G3) and 1 individual in cohort 2 with viral G1. No statistically significant differences were observed either between chronic hepatitis C patients and patients with spontaneous resolution of infection (cohort 1) or between patients with an SR and those with an NSR (cohorts 1 and 2). Nevertheless, a different distribution was observed for individuals bearing haplotype C when patients infected by G1 (66.51%) were compared with both patients infected by non-G1 (26.56%, \( P = 0.024, \text{OR} = 2.35, 95\% \text{CI} = 1.27 \text{ to } 4.33 \)) and the noninfected controls (33.75%, \( P = 0.024, \text{OR} = 1.67, 95\% \text{CI} = 1.17 \text{ to } 2.38 \)). These results were replicated in cohort 2, in which a different distribution was also found for individuals bearing haplotype C when comparing patients infected by G1 (48.83%) with both patients infected by non-G1 (28.42%, \( P = 0.024, \text{OR} = 2.40, 95\% \text{CI} = 1.30 \text{ to } 4.43 \)) and controls (33.75%, \( P = 0.048, \text{OR} = 1.87, 95\% \text{CI} = 1.16 \text{ to } 3.02 \)) (Table 2). These results reflect different viral genotype infection rates among the HAVCR1 haplotypes. Thus, the highest G1 infection rate in cohorts 1 and 2 of chronically infected patients was found among the HAVCR1 haplotypes. Patients bearing haplotype C when patients infected by G1 (45.93%) were compared with both patients infected by non-G1 (26.56%, \( P = 0.024, \text{OR} = 2.35, 95\% \text{CI} = 1.27 \text{ to } 4.33 \)) and the noninfected controls (33.75%, \( P = 0.024, \text{OR} = 1.67, 95\% \text{CI} = 1.17 \text{ to } 2.38 \)). These results were replicated in cohort 2, in which a different distribution was also found for individuals bearing haplotype C when comparing patients infected by G1 (66.51%) with both patients infected by non-G1 (28.42%, \( P = 0.024, \text{OR} = 2.40, 95\% \text{CI} = 1.30 \text{ to } 4.43 \)) and controls (33.75%, \( P = 0.048, \text{OR} = 1.87, 95\% \text{CI} = 1.16 \text{ to } 3.02 \)) (Table 2). These results reflect different viral genotype infection rates among the HAVCR1 haplotypes. Thus, the highest G1 infection rate in cohorts 1 and 2 of chronically infected patients was found among individuals bearing haplotype C (75.82%, \( P_c = 3.2 \times 10^{-4}, \text{OR} = 2.30, 95\% \text{CI} = 1.51 \text{ to } 3.47 \)) and the lowest was found among individuals bearing haplotype D (57.75%, \( P = 0.058 \)), whereas patients bearing haplotypes A and B had intermediate rates of infection by G1 (66.51% and 65.36%, respectively).

### DISCUSSION

In the present study, we found a relationship between the HAVCR1 gene and hepatitis C virus infection. Simultaneous to the identification of the IL28B gene as a gene involved in natural and treatment-mediated viral clearance, the HAVCR1 gene was identified as a candidate gene for HCV clearance in a large-scale study (17). The SNPs rs953569 and rs6880589, located in the HAVCR1 gene region, were found to be associated with natural clearance in European-American and African-American populations, respectively. In the present study, we have tried to replicate the association of rs953569 with spontaneous clearance in two cohorts of Spanish HCV-infected patients, but we could not confirm this association. Additionally, responses to treatment were analyzed, but we did not find any association between rs953569 and clearance after treatment. However, different distributions of rs953569 genotypes were found in cohort 1 among patients infected by different viral genotypes, although this finding could not be confirmed in cohort 2. Results in cohort 1 present a lower rate of infection by viral G1 for individuals with the TT genotype (62%, versus 81% for individuals with the GG and GT genotypes), and the trend is the same in cohort 2 (43% versus 49%). Differences in cohort 2 are not statistically significant, probably because of the number of individuals included (277 in cohort 1 and 181 in cohort 2) and also because of the different rates of infection by G1 in both cohorts (77% in cohort 1 versus 48% in cohort 2). Thus, our findings, together with those previously reported, suggest a relationship between HAVCR1 and HCV infection. The HAVCR1 gene is a gene with an unusual pattern of genetic variation because it is highly polymorphic and, moreover, has numerous non synonymous substitutions and ins/del variants (18). Therefore, it is possible that the gene could be associated with HCV infection outcome, although with different tag SNPs depending on the population studied. In a previous study, we reported 4 major haplotypes of this gene in our population, taking into account haplotypes with both polymorphisms in exon 4 and SNPs. In the same work, we described a “gene expression phenotype” because one of these haplotypes (haplotype B) expresses more mRNA than the others (5). Thus, to better investigate a possible association between the HAVCR1 gene and HCV infection, we classified samples according to these four major haplotypes (5), also including rs953569. We did not find any association between the HAVCR1 haplotypes and natural and treatment-mediated viral clearance; however, we found statistically significantly different viral infection rates among the HAVCR1 haplotypes. Patients bearing haplotype C had the highest G1 infection rates when compared to those of the other patients (\( P_c = 3.2 \times 10^{-4} \)). The difference was not statistically significant with respect to haplotype D, which had the lowest G1 infection rate, probably because of the low frequency of this haplotype in our population. This finding could be the cause of the previously described association between this gene and spontaneous virus clearance, because virus clearance rates may be different depending on viral genotypes. Nevertheless, we cannot discard a bias because of the high rate of infection by G1 in our population; further studies in other populations with higher rates of infection by other viral genotypes are needed to clarify the role of HAVCR1 in HCV infection.

Recently, our group (16) and others (12) reported different rates of infection with different virus genotypes depending on the IL28B genotype. Similar to the results which were found for IL28B, the highest haplotype C frequency and the greatest rates of G1 infection have been described in the African population, whereas the greatest rates of non-G1 infection and the lowest haplotype C frequency have been described in the Asian population (18, 29). Associations between IL28B and viral genotypes could be caused by associations with natural and treatment-mediated clearance; however, according to our results, this is not the case for HAVCR1. We speculate that the resistances of individuals to infection by a particular viral genotype could be different depending on their HAVCR1 haplotypes. If coinfection were a common situation at the beginning of the process, the predominant viral genotype in each individual, and also in each population, would depend in part on the host genetic background. In this sense, Smith et al. (21) described high rates of coinfection by multiple
### TABLE 3 Patient data stratified according to HAVCR1 haplotypes

| Cohort and characteristic | No. of patients with indicated no. of copies of each haplotype (% of total no. of patients) or indicated statistics | A | B | C | D |
|---------------------------|----------------------------------------------------------------------------------------------------------------|---|---|---|---|
| **Cohort 1**              |                                                                                                              |   |   |   |   |
| Spontaneous viral clearance| 140 (50.00)                                                                                                    | 140 (50.00) | 127 (45.35) | 153 (54.65) | 114 (40.71) | 166 (59.29) | 77 (27.50) | 203 (72.50) |
| Chronic hepatitis C        | 38 (55.07) 31 (44.93) NS                                                                                      | 34 (49.27) NS | 27 (39.13) | 42 (60.87) NS | 20 (28.53) | 49 (71.02) NS | 28 (25.00) | 84 (75.00) |
| Sustained response         | 49 (43.75) 63 (56.25)                                                                                        | 49 (43.75) | 63 (56.25) | 52 (46.42) | 60 (53.58) NS | 27 (39.13) | 42 (60.87) NS | 20 (28.53) | 49 (71.02) NS |
| Nonsustained response      | 59 (55.19) 46 (43.81)                                                                                        | 49 (46.66) NS | 56 (53.33) NS | 43 (40.95) | 62 (59.05) NS | 29 (27.61) | 76 (72.39) NS | 20 (28.53) | 49 (71.02) NS |
| G1                        | 107 (51.19) 102 (48.81)                                                                                       | 97 (46.41) | 112 (53.89) | 96 (45.93) | 113 (55.00) | 50 (23.92) | 159 (76.08) NS | 20 (28.53) | 49 (71.02) NS |
| Non-G1                    | 26 (40.62) 38 (59.38)                                                                                        | 29 (45.31) | 35 (54.69) NS | 17 (26.56) | 47 (73.44) | 0.006 | 0.024 | 2.35 (1.27–4.33) | 23 (35.93) | 41 (64.07) NS |
| **Cohort 2**              |                                                                                                              |   |   |   |   |
| Sustained response         | 34 (50.00) 34 (50.00)                                                                                        | 28 (41.17) | 40 (58.83) | 25 (36.76) | 43 (63.24) | 18 (26.47) | 50 (73.53) |
| Nonsustained response      | 29 (50.00) 29 (50.00)                                                                                        | 27 (46.55) | 31 (53.45) NS | 22 (37.93) | 36 (62.07) NS | 10 (17.24) | 48 (82.76) NS | 17 (19.77) | 69 (80.23) |
| G1                        | 42 (48.83) 44 (51.17)                                                                                        | 37 (43.02) | 49 (56.98) | 42 (48.83) | 44 (51.17) | 17 (19.77) | 69 (80.23) |
| Non-G1                    | 49 (51.58) 46 (48.42)                                                                                        | 42 (44.21) | 53 (55.79) NS | 27 (28.42) | 68 (71.58) | 0.006 | 0.024 | 2.40 (1.30–4.43) | 26 (27.36) | 69 (72.64) NS |
| **Cohort 3**              |                                                                                                              |   |   |   |   |
| Control                   | 177 (55.31) 143 (44.69)                                                                                       | 119 (37.18) | 201 (62.81) | 108 (33.75) | 212 (66.25) | 66 (20.62) | 254 (79.37) |
| **Cohort 1 and 2**        |                                                                                                              |   |   |   |   |
| Infection rate by G1      | 149 (66.51) 146 (63.47)                                                                                      | 134 (65.36) | 161 (64.65) | 138 (75.82) | 157 (57.72) | 67 (57.75) | 228 (67.45) |
| Infection rate by non-G1  | 75 (33.49) 84 (36.53)                                                                                        | 71 (34.64) | 88 (35.35) NS | 44 (24.18) | 115 (42.28) | 3.2 × 10⁻⁴ | 2.30 (1.51–4.37) | 49 (42.23) | 110 (57.77) |

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- **Note:** Data of patients were stratified and compared according to whether the patients had spontaneous viral clearance or persistent infection, whether they had a sustained response or a nonsustained response, and whether they were infected with G1 or non-G1.

- **Note:** Compared to control values, $P_c = 0.048$, OR = 1.80, 95% CI = 1.09 to 2.98.

- **Note:** Using genotypes AA, AB, and BB, there were 94 (63.51%) people infected with G1 and 54 (36.49%) people infected with non-G1.

- **Note:** A comparison with genotypes AA, AB, and BB yields a $P_c$ value of 0.024, OR = 1.67, 95% CI = 1.17 to 2.38.

- **Note:** A comparison with genotypes AA, AB, and BB yields a $P_c$ value of 0.048, OR = 1.87, 95% CI = 1.16 to 3.02.
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HCV subtypes and an unstable dynamic, with apparent disappearance and reemergence of variants over a very short time scale in early infections, in serial samples obtained from patients with acute infection.

Our results suggest that the different rates of infection by viral genotypes among HAVCR1 haplotypes depend on differences located in exon 4 and not on differences in mRNA expression because haplotypes A and B, which have the same ins/del combination in this region but different mRNA expression levels, have the same G1 infection rate. In this sense, in a very interesting work recently published, Kim et al. (10) demonstrated an association between 5383_5397ins (named 157insMTTTVP by the authors) and severe liver disease induced by hepatitis A virus (HAV). These authors found a greater cytolytic activity against HAV-infected liver cells in human NKT cells expressing the long form than in those expressing the shorter form. Therefore, association of HAVCR1 with the outcome of HCV infection and other virus infections may be related to NK cell activation.

In conclusion, we have found different viral genotype infection rates among the HAVCR1 haplotypes. This association seems to be based on differences in the mucin domain and could influence susceptibility or resistance to infection by a particular HCV viral genotype.

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