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Epistatic Effects of Immunoglobulin GM and KM Allotypes on Outcome of Infection with Hepatitis C Virus

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Immunoglobulin GM and KM allotypes—genetic markers of γ and κ chains, respectively—are associated with immune responsiveness to several infectious pathogens and with survival in certain viral epidemics. We hypothesized that GM and KM allotypes affect the outcome of hepatitis C virus (HCV) infection. To test this hypothesis, we serologically allotyped 100 persons with well-documented clearance of HCV infection and 198 matched persistently infected persons. None of the GM or KM phenotypes by itself was associated with the clearance or persistence of HCV infection. Particular combinations of these phenotypes, however, were significantly associated with the outcome of HCV infection. Subjects with GM 1,17 5,13 and KM 1,3 phenotypes were over three times (odds ratio [OR], 3.57; 95% confidence interval [CI], 1.44 to 8.87) as likely to clear the infection as the subjects who lacked these phenotypes. This GM phenotype had a similar association with clearance in the absence of KM 3 (OR, 2.75; 95% CI, 1.21 to 6.23). The presence of GM 1,3,17 23 5,13 phenotype (in the absence of KM 3) was associated with persistence (OR, 0.21; 95% CI, 0.06 to 0.77), while its absence (in the presence of KM 1,3) was associated with the clearance of infection (OR, 2.03; 95% CI, 1.16 to 3.54). These results show epistatic interactions of genes on chromosomes 14 (GM) and 2 (KM) in influencing the outcome of an HCV infection. Further investigations involving candidate genes (GM, KM, HLA, and Fcγ receptors) and cellular and humoral immune responses to HCV epitopes are needed to understand the mechanisms underlying these associations.

Hepatitis C virus (HCV) is a major health problem, affecting over 170 million people worldwide (47). Of persons acutely infected with HCV, about 15% spontaneously clear the virus. Among the factors influencing the outcome of HCV infection, the host genetic factors are thought to play a predominant role. Reports from several studies documenting consistent associations of particular HLA alleles with viral persistence and clearance support this contention (40, 41, 43). Allelic variation at the HLA loci, however, accounts for only a small percentage of the total interindividual variation in the outcome of HCV infection (41), suggesting involvement of additional genetic factors that might modify the host immune responsiveness to this pathogen.

Immunoglobulin (Ig) GM and KM allotypes—hereditary antigenic determinants of IgG heavy chains and κ-type light chains, respectively—are associated with viral immunological properties and thus are ideal candidate genetic systems for investigations to identify risk-conferring factors in HCV pathogenesis. GM and KM allotypes are associated with the susceptibility to and outcome of infection by several infectious agents (1–3, 6–13, 21, 23–26, 28–30, 33, 35). GM allotypes are strongly associated with IgG subclass concentrations (19, 22, 27, 34), making them relevant to viral immunity, as the antibody responses to most viral epitopes appear to be IgG subclass (IgG1 and IgG3) restricted (15, 37, 39).

These observations led us to hypothesize that GM and KM allotypes might contribute to the outcome of HCV infection through their possible influence on allotype-restricted antibody responses to the viral antigens. In addition, since particular GM and KM phenotypes have been shown to interact in influencing humoral immunity to certain viral epitopes (1), we wished to determine whether such epistatic interactions were associated with the outcome of HCV infection.

MATERIALS AND METHODS

Study population. Between 1988 and 1989, a cohort was recruited in Baltimore, Md., of persons who had injected illicit drugs in the preceding 10 years, were more than 17 years of age, and were free of manifestations of AIDS (44). Within this cohort, a subset of 1,667 individuals was identified as the HCV subcohort because they had antibodies to HCV and had made at least one follow-up visit. The HCV subcohort was further characterized by serologic test-

TABLE 1. Distribution of GM[a] and KM[b] phenotypes in relation to persistence and clearance of HCV infection

Phenotype(s)	No. (%) of subjects with indicated HCV infection outcome	
	Persistent	Cleared
GM 1,17 5,13	46 (23.5)	31 (31.3)
GM 1,3,17 23 5,13	39 (19.9)	12 (12.1)
GM 1,17 5,13,21	35 (17.9)	13 (13.1)
GM 1,3,17 5,13	20 (10.2)	7 (7.1)
GM 1,3,17 23 5,13,21	13 (6.6)	6 (6.1)
GM 1,17 5,6,13	7 (3.6)	4 (4.0)
Other GM	36 (18.4)	26 (26.3)
KM 1	30 (15.3)	10 (10.3)
KM 3	104 (53.1)	47 (48.5)
KM 1,3	62 (31.6)	40 (41.2)

[a] Persistence, $n = 196$; clearance, $n = 99$; missing GM typing, $n = 3$.
[b] Persistence, $n = 196$; clearance, $n = 97$; missing KM typing, $n = 5$.

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TABLE 2. Distribution of combined GM 1,17 5,13 and KM 1,3 phenotypes in relation to persistence and clearance of HCV infection

Phenotypes	No. (%) of subjects[a] with indicated HCV infection outcome		OR	95% confidence interval	*P*
	Persistent	Cleared			
GM 1,17 5,13 (+)/KM 1,3 (+)	9 (4.6)	15 (15.6)	3.57	1.44–8.87	0.006
GM 1,17 5,13 (+)/KM 1,3 (−)	35 (18.0)	14 (14.6)	0.97	0.46–2.04	0.93
GM 1,17 5,13 (−)/KM 1,3 (+)	53 (27.3)	25 (26.0)	1.12	0.62–2.05	0.70
GM 1,17 5,13 (−)/KM 1,3 (−)	97 (50.0)	42 (43.8)	1.00		

[a] Persistence, $n = 194$; clearance, $n = 96$; missing GM and/or KM typing, $n = 8$.

ing to determine whether HCV infection was ongoing or had cleared (42). An additional 419, 246, and 50 participants were recruited into the cohort in 1994, 1998, and 2000, respectively. For the present study, 100 subjects were selected who had evidence of HCV clearance. For each of these, two controls with persistent HCV infection were selected after matching for race and human immunodeficiency virus (HIV) infection, which were previously associated with HCV clearance in this cohort (42). Cases and controls were also matched for HCV genotype and serotype. Of the members of our cohort, >90% were infected with HCV genotype/serotype 1. To eliminate confounding of results due to HIV infection, only HIV-negative persons were studied. In addition, the analysis was focused on blacks since they comprised more than 90% of the cohort.

Serologic testing. HCV antibody testing was done using expanded- or broad-spectrum HCV 2.0 enzyme immunoassays (EIA) (Ortho Diagnostic Systems, Raritan, N.J.). In antibody-positive sera, HCV RNA was assessed in two samples taken a minimum of 6 months apart. HCV RNA testing was done using a branched-DNA assay (Quantiplex HCV RNA 2.0 assay; Chiron Corporation, Emeryville, Calif.) and an HCV COBAS AMPLICOR system (Roche Diagnostics, Branchburg, N.J.). When HCV RNA in sera from the two visits was classified as undetectable, at least one of the tests used was always the more sensitive HCV COBAS AMPLICOR system. In addition, antibody status was confirmed by a recombinant immunoblot assay (RIBA 3.0) (Chiron Corporation). Subjects with two positive branched-DNA assay results were eligible to be matched to the persons with clearance as controls. HIV type 1 testing was done by EIA, and positive-testing specimens were confirmed by Western blot analysis. Hepatitis B virus surface antigen (HBsAg) status was determined by EIA (AUSZYME; Abbott Laboratories, Abbott Park, Ill.). All assays were performed according to manufacturers' specifications. All samples used for testing had been stored at −80°C after processing, and sera used for RNA testing had not been previously used for other assays.

GM and KM allotyping. Serum samples were typed for G1M (1/a, 2/x, 3/f, and 17/z), G2M (23/n), G3M (5/b1, 6/c3, 13/b3, and 21/g), and KM 1 and KM 3 allotypes by a standard hemagglutination inhibition method (45). In brief, a mixture containing human blood group O Rh^+ erythrocytes coated with anti-Rh antibodies of known GM/KM allotypes, the test sera, and monospecific anti-allotype antibodies was incubated in a microtiter plate. Test sera containing IgG of a particular allotype inhibited hemagglutination by the anti-allotype antibody, whereas negative-testing sera did not. Linkage disequilibrium in the GM system is almost absolute, and the determinants are transmitted as a group called haplotype (38). The notation follows the international system for human gene nomenclature (36), in which haplotypes and phenotypes are written by grouping together the markers that belong to each IgG subclass by the numerical order of the marker and of the subclass; markers belonging to different subclasses are separated by a space, while allotypes within a subclass are separated by commas.

Statistical analysis. Laboratory test results were performed blinded with respect to the outcome and provided to an independent investigator (J.A.), who conducted analyses according to standard statistical methods. Logistic regression models are the most common methods of analyzing predictors of a dichotomous (yes/no) outcome variable. In the present investigation, the dichotomous outcome was defined as clearance or persistence of HCV infection and the prognostic factors were GM and KM allotypes. Conditional logistic regression is a special type of logistic regression, which is used to perform univariate and multivariate analyses for study designs in which cases and controls are matched, as in the present investigation. The PHREG (for "proportional hazard regression") procedure (SAS Institute, Cary, N.C.), which is used to perform conditional logistic regression based on the Cox proportional-hazard regression model, was used to determine the significance (the *P* values) and the strength (the odds ratios [OR]) of the association between GM and KM phenotypes and clearance or persistence of HIV infection. The chi-square test was used to compare the HBsAg prevalence in those who cleared the virus to the prevalence in those who had persistent HCV infection. Statistical significance was defined as $P < 0.05$. Because of almost absolute linkage disequilibrium between particular GM alleles in a given race, data were analyzed as a group (phenotypes) rather than as the presence or absence of individual markers. Furthermore, significant linkage disequilibrium may be the result of certain selective (against immunity to pathogens) evolutionary advantages, making the analysis by phenotypes biologically more meaningful. Subjects with very unusual GM phenotypes were classified as "other" for statistical analyses. Because of the presence of interfering antibodies, eight subjects could not be characterized for particular GM or KM allotypes; these were excluded from the analyses.

RESULTS

A total of 100 persons who cleared HCV infection and 198 matched controls were studied. The median age of persons who had cleared HCV infection (36 years—range, 22 to 62) was similar to the median age of those with persistent infection (36 years—range, 23 to 54). Most subjects were male (clearance group—72%; persistence group—73%). All subjects were HIV negative and black. There was a difference in the percentages of subjects who were positive for HBsAg (20.1% of the clearance group compared with 6.7% of those with viral persistence) ($P < 0.01$), as previously reported (42). (HBsAg testing was not available for 89 persons.)

The distribution of GM and KM phenotypes in relation to

TABLE 3. Distribution of combined GM 1,17 5,13 and KM 3 phenotypes in relation to persistence and clearance of HCV infection

Phenotypes	No. (%) of subjects[a] with indicated HCV infection outcome		OR	95% confidence interval	*P*
	Persistent	Cleared			
GM 1,17 5,13 (+)/KM 3 (+)	28 (14.4)	11 (11.5)	0.90	0.40–2.03	0.80
GM 1,17 5,13 (+)/KM 3 (−)	16 (8.3)	18 (18.8)	2.75	1.21–6.23	0.01
GM 1,17 5,13 (−)/KM 3 (+)	75 (38.7)	35 (36.5)	1.02	0.57–1.83	0.94
GM 1,17 5,13 (−)/KM 3 (−)	75 (38.7)	32 (33.3)	1.00		

[a] Persistence, $n = 194$; clearance, $n = 96$; missing GM and/or KM typing, $n = 8$.

TABLE 4. Distribution of combined GM 1,3,17 23 5,13 and KM 1,3 phenotypes in relation to persistence and clearance of HCV infection

Phenotypes	No. (%) of subjects[a] with indicated HCV infection outcome		OR	95% confidence interval	*P*
	Persistent	Cleared			
GM 1,3,17 23 5,13 (+)/KM 1,3 (+)	17 (8.8)	2 (2.1)	0.26	0.06–1.22	0.09
GM 1,3,17 23 5,13 (+)/KM 1,3 (−)	22 (11.3)	10 (10.4)	1.05	0.45–2.46	0.92
GM 1,3,17 23 5,13 (−)/KM 1,3 (+)	45 (23.2)	38 (39.6)	2.03	1.16–3.54	0.01
GM 1,3,17 23 5,13 (−)/KM 1,3 (−)	110 (56.7)	46 (47.9)	1.00		

[a] Persistence, $n = 194$; clearance, $n = 96$; missing GM and/or KM typing, $n = 8$.

persistence and clearance of HCV infection is given in Table 1. None of the GM or KM phenotypes by itself was associated with the clearance or persistence of HCV infection. Particular combinations of these unlinked genetic systems, however, were significantly associated with the outcome of HCV infection. The GM 1,17 5,13 phenotype significantly interacted with KM 1,3 and KM 3 phenotypes. Subjects with GM 1,17 5,13 and KM 1,3 phenotypes were over three times (OR = 3.57) as likely to clear the infection as the subjects who lacked both these phenotypes (Table 2). This GM phenotype had a similar association with clearance in the absence of KM 3 (OR = 2.75) (Table 3).

Likewise, the GM 1,3,17 23 5,13 phenotype significantly interacted with KM 1,3 and KM 3 phenotypes. Individuals who lacked this GM phenotype (but were positive for KM 1,3) were over twice (OR = 2.03) as likely to clear the infection as the subjects who lacked both these phenotypes (Table 4). In the absence of KM 3, however, this GM phenotype was associated with the persistence of infection: subjects lacking KM 3 (but positive for GM 1,3,17 23 5,13) were about 79% (OR = 0.21) less likely to clear the infection than those who lacked both phenotypes (Table 5). No other significant associations were found.

DISCUSSION

We have shown nonadditive interactive effects of two separate genetic regions—GM allotypes (coded by genes located on chromosome 14) and KM allotypes (coded by genes on chromosome 2)—on the outcome of HCV infection. There are at least two possible explanations for the associations. The GM and KM allotypes could themselves affect the outcome of HCV infection. Alternatively, linkage disequilibrium between particular GM or KM alleles and the alleles of another putative risk-conferring locus for HCV pathogenesis might give rise to the associations observed.

One mechanism by which GM and KM allotypes could influence the outcome of HCV infection is by regulating the titer and affinity of neutralizing antibodies directed against viral epitopes. Perhaps the B-cell receptors with the KM 1,3 and GM 1,17 5,13 specificities are more compatible with HCV epitopes—and thus provoke a vigorous humoral immunity and clear the infection—whereas those carrying GM 1,3,17 23 5,13 and non-KM 3 determinants form a less compatible receptor for the critical epitopes of this agent and remain persistently infected. Similar mechanisms can be envisioned for other significant associations observed. Studies to determine the influence of GM and KM allotypes on the qualitative and quantitative expression of anti-HCV antibodies may provide new insights into understanding the mechanisms underlying these associations.

Since this is the first study of this type for HCV infection, these results cannot be compared directly with those of other studies. Nonetheless, interactive effects of particular GM and KM phenotypes observed in this study are reminiscent of those reported for humoral immune responses to the Epstein-Barr virus and group B streptococcus antigens and cellular immune responses to the streptococcal cell wall antigens (1, 24, 46). Significant interaction between particular GM and KM phenotypes may be a reflection of preferential association of heavy and light chains of particular genotypes in the synthesis of an antibody molecule. Such nonrandom pairing of heavy and light chains has been reported for experimental animals (5, 31).

Although GM and KM markers are located on the constant region, there is a growing body of evidence for the involvement of these regions in antibody specificity usually associated with the variable region of the Ig molecule. Possible mechanisms include direct contribution to the formation of idiotypic determinants, modulation of antibody binding affinity, and linkage disequilibrium with alleles coding for the variable-region epitopes. Amino acids encoded by the variable region and the adjoining CH1—where allelic determinants G1M 3 and 17 are located—may directly form idiotypic determinants. Alterna-

TABLE 5. Distribution of combined GM 1,3,17 23 5,13 and KM 3 phenotypes in relation to persistence and clearance of HCV infection

Phenotypes	No. (%) of subjects[a] with indicated HCV infection outcome		OR	95% confidence interval	*P*
	Persistent	Cleared			
GM 1,3,17 23 5,13 (+)/KM 3 (+)	20 (10.3)	9 (9.4)	0.62	0.25–1.57	0.31
GM 1,3,17 23 5,13 (+)/KM 3 (−)	19 (9.8)	3 (3.1)	0.21	0.06–0.77	0.02
GM 1,3,17 23 5,13 (−)/KM 3 (+)	83 (42.8)	37 (38.5)	0.64	0.37–1.11	0.11
GM 1,3,17 23 5,13 (−)/KM 3 (−)	72 (37.1)	47 (49.0)	1.00		

[a] Persistence, $n = 194$; clearance, $n = 96$; missing GM and/or KM typing, $n = 8$.

tively, differential folding of the constant domains carrying particular GM markers may result in different tertiary structures in the variable region, giving rise to different idiotypes. These idiotypes may act as recognition structures for regulatory T cells—some with an affinity for the helper and others with an affinity for the suppressor T cells—resulting in enhancement or suppression of particular antibodies. Contribution of both constant and variable regions in the formation of idiotypic determinants has been clearly documented for the T15 system in mice, and such isotype-restricted idiotypes have been postulated to be involved in the regulation of class-specific antibody responses (18). Significant linkage disequilibrium between particular variable and constant genes may provide yet another mechanism for the constant region determinants to indirectly influence (by "hitchhiking" with the variable-region markers) antibody responses controlled primarily by the variable genes. Both KM 1 and KM 3 alleles are associated with different variable-region determinants of the κ chain (20). Similar relationships may exist between particular variable and constant alleles of the γ chain as well. Although the underlying mechanisms are not completely understood, there are several well-documented examples of constant domains influencing the specificity of antibodies to various antigens (4, 17, 32).

As the bulk of published data suggests that the vigor and breadth of adaptive T-cell responses contribute substantially to recovery from HCV infection, it is important to consider possible mechanisms for the involvement of GM allotypes in cellular immunity (16, 46). One mechanism could operate through their interaction with the Fcγ receptors (FcγR) (35). All GM epitopes—with the exception of G1M 3 and 17—are present on the Fc portion of the IgG molecule. Thus, Fc of a particular GM genotype could preferentially associate with the FcγR of a particular genotype and influence the outcome of HCV infection through inhibition or induction of cytotoxic T lymphocytes specific for this virus. FcγR have been implicated in the reduced induction of HCV-specific cytotoxic T lymphocytes (14).

The role of HLA genes in the persistence and clearance of HCV infection is well established. Simultaneous examination of HLA, GM, KM, Fcγ, and killer Ig-like receptor genes may shed some light on the possible epistatic effects of these genetic systems on the outcome of HCV infection. This is the first report (to our knowledge) implicating GM and KM allotypes in immunity to HCV.

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