Published in final edited form as:

Hum Immunol. 2012 March ; 73(3): 263–266. doi:10.1016/j.humimm.2011.12.008.

Epistatic Interactions between Fc (GM) and FcγR Genes and the Host Control of HIV Replication

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Abstract

Host genetic factors are thought to contribute to the interindividual differences in the control of HIV replication. The aim of the present investigation was to determine whether genes encoding GM and KM allotypes—genetic markers of immunoglobulin γ and κ chains, respectively—and those encoding Fcγ receptor (FcγR) IIa and IIIa are associated with the host control of HIV replication. A case-control design was employed amongst HIV-infected subjects, with a group that spontaneously controlled HIV replication (“controllers”) as cases (n=73) and those who did not control replication, as controls (n=100). Genotyping was done by PCR-RFLP, direct DNA sequencing, and TaqMan® genotyping assays. In Caucasian Americans, certain combinations of FcγR and GM genotypes were differentially distributed between controllers and non-controllers. Among the non-carriers of FcγRIIa arginine allele, GM21 non-carriers had over seven-fold greater odds of being controllers than the carriers of this allele (OR=7.47). These GM determinants also interacted with FcγRIIIa alleles. Among the carriers of the FcγRIIIa valine allele, GM21 non-carriers had over three-fold greater odds of being controllers than the carriers of this allele (OR=3.26). These results show epistatic interactions of genes on chromosomes 14 (GM) and 1 (FcγR) in influencing the control of HIV replication.

Keywords

GM allotypes; KM allotypes; FcγR; ADCC; HIV

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1. Introduction

HIV infection affects approximately 33.3 million people worldwide and is characterized by severe loss of CD4+ T-cells over several years leading to acquired immune deficiency syndrome (AIDS). Without highly active antiretroviral therapy, the mean time to the development of AIDS for an infected individual is 7.7–11 years after initial seroconversion depending on age [1]. A small percentage (<1) of HIV infected people naturally control HIV replication, i.e., they are able to maintain plasma viral loads below 2000 RNA copies/mL without antiviral treatment. Understanding the mechanisms of successful viral control could lead to the development of novel immunotherapeutic strategies against this infection. Among the factors influencing the outcome of HIV infection, the host genetic factors—especially genes of the immune system—are thought to play a predominant role. Results of the recent International HIV Controllers Study support this contention [2]. In this large multiethnic genome-wide association study (GWAS), all single nucleotide polymorphisms significantly associated with HIV control mapped within the HLA complex. Allelic variation at the HLA loci, however, accounted for <20% of the observed variance of host control, suggesting involvement of additional genetic factors that may modify the host immune responsiveness to this pathogen.

Antibody-dependent cell-mediated cytotoxicity (ADCC) is a prominent mechanism underlying the relative protection provided by anti-HIV antibodies [3,4]. ADCC is triggered upon ligation of FcγR to the Fc of IgG molecules. It follows that genetic variation in FcγR and Fc could contribute to the interindividual differences in ADCC, resulting in differential host control of HIV replication. Genetic variants of IgG γ chains are called GM allotypes, encoded by three very closely linked genes on chromosome 14. GM allotypes are expressed on the constant region of γ1, γ2, and γ3 chains. All GM determinants, with two exceptions, are expressed on the Fc region of γ chains [5]. Linkage disequilibrium between particular GM alleles is almost absolute within a race and the determinants are transmitted as a group (haplotypes). Each major race has a distinct array of GM haplotypes [6]. Polymorphic determinants of FcγRIIa and FcγRIIIa, encoded by genes on chromosome 1, have been shown to influence HIV susceptibility and disease progression [7–9], but the role of GM determinants in HIV virologic control has not been investigated. Similarly, the role of KM allotypes (κ-chain determinants on chromosome 2), which are associated with susceptibility to many infectious diseases [10–13], in the outcome of HIV infection has not been investigated.

Genes do not act in isolation: there is growing body of evidence that epistasis—modification of the action of a gene by one or more other genes—plays a significant role in determining the rate of progression to AIDS [14]. Determinants expressed on Fc (GM) and FcγR are probably some of the most likely ligand-receptor candidate pairs for gene-gene interactions in the human genome. Thus, the aim of this investigation was to determine whether particular GM, KM, FcγRIIa, and FcγRIIIa genotypes were individually or epistatically associated with the host control of HIV replication.

2. Materials and Methods

2.1 Study subjects

Informed consent was obtained from study subjects enrolled in the Study of the Consequences of Protease Inhibitor Era (SCOPE) cohort at the University of California, San Francisco. The study protocol was approved by the Institutional Review Board for human research at respective institutions. Blood was collected from a total of 73 HIV-infected controllers (40 Caucasian Americans, 33 African Americans) and 100 HIV-infected non-controllers (74 Caucasian Americans, 26 African Americans). Controllers were classified as

those individuals that were chronically infected for more than one year, naïve to antiretroviral therapy, and had three documented plasma HIV RNA levels < 2,000 copies/mL over at least a 12-month period [15]. Non-controllers were classified as those individuals that were chronically infected for more than one year, had no antiretroviral therapy for one year preceding sample collection, and had HIV RNA levels > 10,000 copies/mL [15]. The demographic and the clinical characteristics of the study population are presented in Table 1.

2.2 GM, KM, and FcγR genotyping

DNA was isolated using a standard protocol (Qiagen-Kit method)—IgG1 allelic markers GM3 and GM17 (arginine to lysine substitution, a G→A transition in the CH1 region of the γ1 gene) were determined by direct DNA sequencing. PCR was used to amplify the CH1 region of the γ1 gene using the following primers: 5'-CCCCTGGCACCTCCTCCAA-3' and 5'-GCCCTGGACTGGGGCTGCAT-3' [16]. The double-stranded 364 bp DNA product was then purified and sequenced on an ABI Prism 377.

IgG2 allelic marker GM23 (valine-to-methionine substitution, a G→A transition in the CH2 region of the γ2 gene) was determined using a nested PCR-RFLP method. A 915 bp fragment that includes the polymorphic site was amplified using the following primers: 5'-AAATGTTGTGTCGAGTGCCC-3' and 5'-GGCTTGCCGGCCGTGGCAC-3' [17]. A 197 bp fragment was then amplified from the 915 bp fragment using the following primers: 5'-GCACCACCTGTGGCAGGACC-3' and 5'-TTGAACTGCTCCTCCCGTGG-3'. The 197 bp product was digested by the restriction enzyme NlaIII. This resulted in the following product sizes for each genotype: GM23(+/+), 90 bp, 63 bp, and 44 bp; GM23(-/-), 134 bp and 63 bp; and GM23(+/-), 134 bp, 90 bp, 63 bp, and 44 bp.

IgG3 hetero-allelic markers GM5 (asparagine-to-serine substitution, an A→G transition in the CH3 region of the γ3 gene) and GM21 (proline-to-leucine substitution, a C→T transition in the CH2 region of the γ3 gene) were determined using a PCR-RFLP method. A 765 bp fragment that includes the polymorphic sites was amplified using the following primers: 5'-CTGAACTCCTGGCAGGACCGT-3' and 5'-GCTTGCCGGCTATCGCACTC-3'. A 685 bp fragment was then amplified from the 765 bp fragment using the following primers: 5'-ACCCAAGGATACCCTTATGATT-3' and 5'-GAGGCTCTTCTGCGTGAAGC-3' [18]. The 685 bp product was digested by the restriction enzyme MspAII. This resulted in the following product sizes for each genotype: GM5/5, 171 bp, 158 bp, 156 bp, 137 bp, and 63 bp; GM21/21, 327 bp, 295 bp, and 63 bp; and GM5/21, 327 bp, 295 bp, 171 bp, 158 bp, 156 bp, 137 bp, and 63 bp.

The κ-chain is triallelic—KM1, KM1,2, and KM3 alleles. KM1 allele is rare; 98% of the individuals positive for KM1 are also positive for KM2. Thus, positivity for KM1 includes both KM1 and KM1,2 alleles. The KM alleles were determined by a previously described PCR-RFLP method [19].

A change in the nucleotide at position 497 of FcγRIIa gene from A to G results in change of amino acid histidine to arginine (H/R131). A change in the nucleotide at position 559 of the FcγRIIIa gene from T to G results in phenylalanine to valine substitution (F/V158) in the membrane proximal IgG like domain of FcγRIIIa. The FcγRIIa alleles were determined by a previously described PCR-RFLP method [20]. The FcγRIIIa alleles were determined by the TaqMan® SNP Genotyping Assays supplied by Applied Biosystems, following manufacturer's protocols.

Due to technical reasons, certain samples were not typed for certain genotypes causing slight variations in the sample number for each genotype.

2.3 Statistical Analysis

Fisher's exact tests were used to determine the significance of the genotype frequency differences between controllers and non-controllers. Dominant and recessive tests of the genetic effects were constructed; however, due to low minor allele frequencies some models were not explored. All interaction effects were tested in logistic regression models that also allowed for main effects of the genes. Interaction tests were constructed as 1 degree of freedom tests, assuming either recessive or dominant genetic effects of each genetic marker. All tests were two-tailed with an $\alpha = 0.05$ level. Due to varying genotype frequencies across European ancestry and African ancestry populations, tests of differences in genotype frequencies and gene-gene interactions were conducted separately for Caucasian and African American subjects in the cohort. In total main effects of six loci and eight possible interactions between the four GM/KM loci and two Fc γ R loci were explored. Because of multiple testing, the findings could be due to chance fluctuations, as the p values for the associations were not adjusted by Bonferroni's method. Such adjustment is controversial and we believe that, instead of performing such adjustment in this work, the best approach would be to test in an independent sample.

3. Results

The distribution of GM, KM, and Fc γ R genotypes in HIV controllers and non-controllers is given in Table 2. None of the genotype frequencies by itself differed significantly between the two groups. However, in Caucasian Americans, certain combinations of Fc γ R and GM genotypes were differentially distributed between controllers and non-controllers (Table 3). Among Fc γ RIIa R non-carriers (i.e. H/H homozygotes), GM21 non-carriers (i.e. GM5 homozygotes) had over seven-fold greater odds of being controllers than the carriers of this allele (OR = 7.47; $p = 0.0214$). Testing epistasis between Fc γ RIIa and GM21 in a logistic regression model, the interaction was statistically significant ($p = 0.0255$). These GM determinants also interacted with Fc γ RIIIa alleles. Among the carriers of the Fc γ RIIIa V allele, GM21 non-carriers had over three-fold greater odds of being controllers than the carriers of this allele (OR = 3.26; $p = 0.0495$). Testing epistasis between Fc γ RIIIa and GM21 in a logistic regression model, the interaction was trending towards statistical significance ($p = 0.0503$). Among Fc γ RIIa R-carriers and Fc γ RIIIa V non-carriers, the GM21 genotype frequencies between controllers and non-controllers were not significantly different ($p = 0.817, 0.560$, respectively). There was no association between HIV control and epistatic interactions between Fc γ RIIa and Fc γ RIIIa alleles and GM3, GM17 or GM23 determinants. Also, no significant associations were observed in African American subjects.

4. Discussion

The results reported here show significant interactive effects of particular Fc γ R and GM genotypes on the host control of HIV replication. A plausible mechanism underlying this association could involve epistatic contribution of these loci to the ADCC of HIV-infected cells or to the antibody-dependent cell-mediated virus inhibition (ADCVI). The interacting Fc γ RIIa and Fc γ RIIIa alleles—H and V, respectively—are high affinity alleles, that is, they bind the Fc region of IgG antibodies better than their allelic counterparts [21,22]. Alleles at both loci have been shown to be risk factors for HIV infection and progression, but no consistent pattern has emerged [7,9,23], which could be due to the fact that all studies thus far have examined the genes encoding the receptors, but not those coding for their ligand (Fc/GM). Results reported here underscore the importance of simultaneously examining the ligand (GM) and the receptor (Fc γ R) genes for their possible contribution to the host control

of HIV replication. It is possible that GM5-expressing anti-HIV IgG antibodies have higher affinity for the FcγRIIa H and FcγRIIIa V alleles, which could enhance the magnitude of ADCC against HIV-infected cells, leading to a better control of HIV replication. This is analogous to the reported allelic interaction between particular killer cell immunoglobulin-like receptors and their HLA-C ligand in the resolution of hepatitis C virus infection [24]. In addition to ADCC and ADCVI, other Fc-mediated effector functions (e.g. phagocytosis) could also explain the findings of this investigation.

We did not find an interactive effect of GM and FcγR alleles on the control of HIV replication in the African American cohort. The reasons for these racial differences are not clear. The inability to detect an association in this group could be due to its relatively small size. Alternatively, GM and FcγR alleles could interact with the allelic determinants of another as-yet-undetermined gene whose frequencies are different in the two populations. There are marked qualitative and quantitative differences in the distribution of GM alleles among various racial groups [6]. Due to the unavailability of satisfactory molecular methods, not all GM alleles were examined in this investigation. Examination of certain race specific alleles (e.g. GM 6) could contribute to our understanding of the mechanisms of successful viral control in African Americans.

If GM and FcγR genes contribute to the host control of HIV replication, as suggested by the results presented here, why have they not been detected by the GWAS of HIV control? One likely reason is the absence of GM genes in the HapMap panel [25]. IgG gene segments harboring GM genes are highly homologous and apparently not amenable to the high throughput genotyping technology used in GWAS. Another contributing factor might be the inability of most GWAS to detect epistatic interactions [26]. Therefore, a candidate gene approach involving a large sample size would be necessary to confirm and extend the findings from this study. If confirmed, they suggest further experiments to delineate the mechanisms underlying this association, such as determining the possible differential contributions of Fc (GM) and FcγR alleles to the ADCC of cells expressing HIV envelope proteins. Evidence for the involvement of these loci in the ADCC of cells expressing tumor antigens [27–29] provides further rationale and impetus for such studies. Results from such studies could significantly impact both active (vaccine) and passive (antibody-based) immunotherapies against this infection.

Acknowledgments

This work was supported in part by the National Institutes of Health (grants P30 AI27763 and UL1 RR024131).

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Table 1

Study population demographic and clinical characteristics

Characteristic	All	Controllers	Non-Controllers
Caucasian Americans	114	40 (35.0)	74 (65.0)
African Americans	59	33 (55.9)	26 (44.1)
Males	148	58 (39.2)	90 (60.8)
Females	25	15 (60)	10 (40)
Age at blood collection, years	50.6 ± 8.7	49.6 ± 9.0	51.3 ± 8.4
Duration of Infection, years	15.1 ± 6.8	12.8 ± 6.8	16.7 ± 6.8
HBV Positive	97	46 (47.4)	51 (52.6)
HCV Positive	64	40 (62.5)	24 (37.5)
CD4 Cell Count, cells/mm ³	600.7 ± 368.2	785.0 ± 374.2	466.1 ± 368.1

NOTE. Data are no. (%) or mean ± standard deviation

Table 2
Distribution of GM, KM, and FcγR genotypes among HIV controllers and non-controllers

Genotypes	Caucasian Americans				African Americans			
	Controllers		Non-Controllers		Controllers		Non-Controllers	
	n	%	n	%	n	%	n	%
GM3/3	18	45.0	27	36.5	2	6.1	1	3.8
GM3/17	17	42.5	38	51.4	7	21.2	6	23.1
GM17/17	5	12.5	9	12.2	24	72.7	19	73.1
GM23(+/+)	7	17.5	14	18.9	2	6.1	1	3.8
GM23(+/-)	18	45.0	29	39.2	3	9.1	5	19.2
GM23(-/-)	15	37.5	31	41.9	28	84.8	20	76.9
GM5/5	19	47.5	28	38.9	28	84.8	23	88.5
GM5/21	16	40.0	35	48.6	5	15.2	3	11.5
GM21/21	5	12.5	9	12.5	0	0.0	0	0.0
KM1/1	1	2.5	0	0.0	4	12.1	4	15.4
KM1/3	4	10.0	18	24.3	9	27.3	12	46.2
KM3/3	35	87.5	56	75.7	20	60.6	10	38.5
FcγRIIa H/H	10	25.0	21	28.8	5	15.2	5	19.2
FcγRIIa H/R	18	45.0	37	50.7	12	36.4	12	46.2
FcγRIIa R/R	12	35.0	15	20.5	16	48.5	9	34.6
FcγRIIa V/V	5	12.8	7	9.9	1	3.0	3	11.5
FcγRIIa F/V	13	33.3	34	47.9	17	51.5	12	46.2
FcγRIIa F/F	21	53.8	30	42.3	15	45.5	11	42.3

Table 3

Distribution of particular FcγR-GM genotype combinations in Caucasian Americans in relation to HIV control status

FcγR Genotype	G-M Genotype	Controllers		Non-Controllers		p	OR (95% CI)
		n	%	n	%		
FcγRIIa R non-carriers	GM21 non-carriers	7	70	5	23.8	0.0214	7.47 (1.39 – 40.2)
	GM21-carriers	3	30	16	76.2		
FcγRIIa R-carriers	GM21 non-carriers	12	40	23	45.1	0.817	0.811 (.325 – 2.03)
	GM21-carriers	18	60	28	54.9		
FcγRIIIa V non-carriers	GM21 non-carriers	7	33.3	13	44.8	0.560	0.615 (.192 – 1.97)
	GM21-carriers	14	66.7	16	55.2		
FcγRIIIa V-carriers	GM21 non-carriers	11	61.1	13	32.5	0.0495	3.26 (1.03 – 10.4)
	GM21-carriers	7	38.9	27	67.5		