HLA Class I and *KIR* Genes Do Not Protect Against HIV Type 1 Infection in Highly Exposed Uninfected Individuals With Hemophilia A

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A recent genome-wide association study (GWAS) involving patients with hemophilia A who were exposed to but uninfected with human immunodeficiency virus type 1 (HIV-1) did not reveal genetic variants associated with resistance to HIV-1 infection, beyond homozygosity for *CCR5*-Δ*32*. Since variation in *HLA* class I and *KIR* genes is not well interrogated by standard GWAS techniques, we tested whether these 2 loci were involved in protection from HIV-1 infection in the same hemophilia cohort, using controls from the general population. Our data indicate that *HLA* class I alleles, presence or absence of *KIR* genes, and functionally relevant combinations of the *HLA*/*KIR* genotypes are not involved in resistance to parenterally transmitted HIV-1 infection.

Keywords. HESN; hemophilia; HIV-1; HLA; KIR.

Hemophilia A is the most common inherited bleeding disorder and is caused by deficiency of coagulation factor VIII (FVIII) [1]. The deficiency results from deleterious mutations in the gene encoding FVIII, located on chromosome X. The incidence of the disease is 1 in 5000 male live births, occurring as mild, moderate, or severe forms, depending on the residual level of FVIII activity. Prevention of hemorrhagic episodes involves intravenous infusions of FVIII, which have to be administered on a regular basis and at high frequency in patients with severe forms of the disease. Before the introduction of recombinant FVIII in the 1990s, donor-derived pooled plasma concentrates were the only sources of therapeutic FVIII. These concentrates were not treated for virus inactivation until 1984, and as a result, >90% of patients with hemophilia A who received high- and moderate-dose treatments between 1978 and 1984 were infected with HIV-1 [2]. The uninfected minority from this patient group, along with other cohorts of HIV-exposed seronegative (HESN) individuals exposed to the virus by various routes, represent a source of important genetic material for studying natural resistance to HIV acquisition [3].

Attempts to identify the genetic basis for resistance to HIV infection have only demonstrated consistent results for the locus encoding the chemokine receptor CCR5, which also serves as a coreceptor for R5-tropic viral isolates [4]. Homozygosity for a 32-bp deletion (Δ32/Δ32) in the *CCR5* gene, which occurs virtually only in white individuals, results in abrogation of the receptor's cell surface expression. Up to 15% of hemophiliac HESN individuals carry the Δ32/Δ32 genotype, compared with approximately 1% of the general white population. A rarer mutation, m303, which introduces a premature stop codon, has a similar effect on CCR5 production, and homozygous (m303/m303) or compound heterozygous (m303/Δ32) carriers have also been observed among HESN individuals.

A genome-wide association study (GWAS) was recently performed to search for additional genes involved in resistance to HIV infection in patients with hemophilia A [5]. No variants tested in 431 HESN individuals and 765 HIV-infected controls reached genome-wide significance. Here, we applied a candidate-gene approach to the same cohort of hemophiliac HESN individuals and tested variation at 2 loci that are known to be involved in HIV pathogenesis, the gene clusters encoding HLA class I and the killer cell immunoglobulin-like receptor (KIR) [6]. Variation in the *HLA* class I region shows the strongest and most consistent influence on the course of HIV disease, including allelic associations with protection (*B*57* and *B*27*) and susceptibility (*B*35* subtypes), as well as the allele-defined level of *HLA-C* expression. These associations are thought to be due primarily to effective anti-HIV cytotoxic T-lymphocyte responses. Interactions between KIR and HLA regulate innate immune responses of natural killer (NK) cells and a subset of $CD8^+$ T cells. A given *KIR* gene recognizes a specific set of HLA allotypes, and certain combinations of *KIR3DL1/S1* and *HLA-B* alleles have been shown to delay disease progression [6].

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Variation at the *HLA* and *KIR* loci is usually not extensively tested by standard GWAS, because most *HLA* alleles are not efficiently tagged by any single-nucleotide polymorphism (SNP) present on the genotyping arrays [7] and because of the extreme insertion/deletion polymorphism within the *KIR* locus. Given the importance of *HLA* and *KIR* for both innate and acquired immunity, we tested whether variation within these loci may influence HIV acquisition as they do for post-infection events. In contrast to the Lane et al study [5], we used individuals randomly drawn from the general population as controls in order to avoid the frailty bias that is inherent to virtually all HIV+ cohorts (ie, the enrichment of alleles associated with better HIV control in cohorts of chronic patients, due to longer survival which confounds association results [8]). Use of a random control population is essential when probing for an effect of *HLA* on HIV infection, since the *HLA* class I is the only locus genome-wide to consistently show an effect on control of HIV after infection.

METHODS

Study Subjects

HESN individuals with hemophilia A were included in the CHAVI014 protocol and described previously [5]. Briefly, these individuals had moderate or severe hemophilia A, had been treated with plasma-derived FVIII concentrates between 1979 and 1984, and were negative for HIV. The control group included individuals from the 1958 birth cohort (available at: http://www2.le.ac.uk/projects/birthcohort, accessed 17 April 2014). The 1958 birth cohort provides a geographically representative sample of British people primarily of European ancestry and has been used in a number of genetic case-control studies. Institutional review boards at each participating center approved the study, and all participants provided informed consent for genetic testing.

Genotyping

The GWAS data (Illumina 1M) and the 2-digit *HLA* class I genotypes for the 1958 birth cohort were obtained from the Wellcome Trust Case Control Consortium (available at: http://www.wtccc.org.uk/, accessed 17 April 2014). The GWAS data (Illumina 1M/1Mduo) for the HESN individuals were collected previously [5]. The *HLA* class I loci were typed by the sequence-based typing method recommended by the 13th International Histocompatibility Workshop (available at: http://www.ihwg.org, accessed 17 April 2014). *HLA* sequences were analyzed using Assign software (Conexio Genomics), which matches experimental data to known allele sequences from the International Immunogenetics Information System database (available at: http://www.ebi.ac.uk/imgt/hla, accessed 17 April 2014). *KIR* genotyping for the presence or absence of each gene was conducted by polymerase chain reaction (PCR) with sequence-specific priming as described previously [9], with some modifications. PCR was conducted using 5 ng of genomic DNA in a volume of 5 μL, using SYBR Green Master Mix with Platinum Taq (Life Technologies). The presence or absence of specific PCR products was detected by melting curve analysis on the 7900 Real-Time PCR System (Applied Biosystems). Additional *KIR2DS4* subtyping for the presence of a 20-bp deletion resulting in a null allele was resolved by size discrimination, using the LabChip GX instrument (Perkin Elmer).

Statistical Analyses

We conducted quality control analysis of the GWAS data as described earlier [5]. Logistic regression tests were performed using R software (available at: http://www.r-project.org, accessed 17 April 2014). To avoid spurious associations due to population stratification, we used the Eigenstrat method [10]: after exclusion of population outliers, genetic association tests were corrected for residual stratification, using the coordinates of the significant principal components axes as covariates. Bonferroni correction was used to calculate the significant P value threshold, $P = .0006$. Because of linkage disequilibrium, not all tests are independent. Therefore, we also calculated an alternative significance threshold that was based on permutation tests. For this, we randomly attributed case or control status to each of the study subjects and repeated all logistic regression tests. With 1000 permutations, the lowest 5% of P values were <.0009. Therefore, the significance threshold based on permutations ($P = .0009$) was very close to that calculated by the Bonferroni method ($P = .0006$). To minimize the risk of false associations, we used the most stringent threshold, although it did not make any difference. Power calculations are provided in Supplementary Table 1.

RESULTS AND DISCUSSION

DNA samples were available for 442 of 483 HESN individuals included in the CHAVI014 protocol [5]. These were genotyped for *HLA* class I alleles and the presence or absence of the *KIR* genes. A total of 117 individuals were excluded from further analyses on the basis of the following criteria: *CCR5* mutation homozygosity (either Δ32 or m303), self-reported non-European ethnicity, GWAS quality control, relatedness, population outliers, and genotyping failure. Thus, 325 white HESN individuals with GWAS, *KIR*, and *HLA* class I data were used as cases in genetic tests. The controls represent the general British population, and genotypes available for these samples included GWAS, *HLA* class I, and *KIR* (GWAS/*HLA-A*, 1916 samples; GWAS/*HLA-B*, 1882; GWAS/*HLA-C*, 1602; GWAS/*KIR*, 1305; GWAS/*HLA-A*/*KIR*, 1187; GWAS/*HLA-B*/*KIR*, 1176; and GWAS/*HLA-C*/*KIR*, 855).

No SNP reached genome-wide significance when the HESN individuals were compared with the general population

controls, similar to the results of the study by Lane et al, in which HIV–infected individuals were used as controls [5]. Next, the frequencies of the *HLA* class I alleles were compared between the HESN individuals and individuals in the 1958 birth cohort in dominant models using logistic regression. Although some differences in allelic frequencies were observed between cases and controls, none reached statistical significance after correction for population stratification and multiple testing (Table 1). For example, *HLA-B*08* was present at only about half the frequency in the HESN individuals as compared to individuals in the 1958 birth cohort (15% vs 27%), but this difference is entirely attributed to differences in population structure between cases and controls. The HESN group contains a mix of Europeans with substantial numbers of individuals from southern Europe, whereas the 1958 birth cohort is a relatively homogeneous British population. The *HLA-B*08* allele is observed at a lower frequency in southern Europe as compared to northern Europe, such that the difference between the cases and controls is geographically based, as indicated by the statistical analysis (available at: http://www.allelefrequencies.net, accessed 17 April 2014).

Similarly, we tested the frequencies of the *KIR* genes (presence or absence), using logistic regression. Again, no significant difference between cases and controls was observed (Table 2). Given the known receptor-ligand interactions between HLA and KIR, we further performed tests for KIR ligand groupings and genotypic combinations, some of which have been associated with diseases previously (Table 2 and Supplementary Table 2). These included *KIR3DL2-HLA-A*3/11*, functional *KIR2DS4-HLA-A*3/11*, *KIR3DL1-HLA-Bw4*, *KIR3DS1-HLA-Bw4-80I*, *KIR2DL3-HLA-C1*, and *KIR2DL1/S1-HLA-C2* [6]. None of the results were significant after correction for multiple testing, but the lowest *P* values were observed for the *KIR2DL1-HLA-C2* compound genotype (adjusted odds ratio, 1.68; $P = .002$), which tends toward protection from HIV infection. This genotype confers a relatively high level of inhibitory KIR engagement and may be indicative of efficient NK-cell licensing. However, the possibility of such a mechanism being involved in protection from infection is inconclusive from our data, as the *P* value does not reach the threshold of significance ($P = .0006$).

Thus, we did not detect any significant influence of the *HLA* class I alleles and the presence or absence of the *KIR* genes on HIV acquisition among the hemophiliac HESN individuals. Whereas homozygosity for deleterious *CCR5* variants is protective against mucosal and parenteral transmission of HIV, there could be distinct genetic mechanisms of protection against HIV infection, depending on the route of exposure, and it is well documented that the level of viral exposure impacts the risk of infection [3]. These factors vary across groups who are at risk for HIV infection, including sex workers, serodiscordant couples, children of infected mothers, injection drug users, men who have sex with men, and health workers [3]. The exposure level

Table 1. Logistic Regression Analysis Comparing 325 Hemophiliac Human Immunodeficiency Virus–Exposed Seronegative Individuals (Cases) and 1916 Individuals From the 1958 Birth Cohort (Controls) for *HLA* Class I Alleles With Frequencies >3%

HLA Allele	Cases, % (No.)	Controls, % (No.)	*P* Value	Adjusted OR (95% CI)
A*01	24.3 (79)	34.4 (660)	.53	0.90 (.66–1.24)
A*02	52.3 (170)	49.7 (953)	.08	1.30 (.97–1.73)
A*03	23.1 (75)	26 (499)	.35	0.85 (.61–1.19)
A*11	8.9 (29)	12.5 (239)	.09	0.66 (.41–1.07)
A*23	4.0 (13)	3.0 (57)	.62	1.20 (.58–2.45)
A*24	17.8 (58)	14.9 (286)	.83	0.96 (.65–1.41)
A*25	3.1 (10)	3.5 (67)	.54	0.78 (.34–1.75)
A*26	7.7 (25)	4.9 (93)	.94	0.98 (.50–1.89)
A*29	8.3 (27)	7.9 (152)	.97	1.01 (.59–1.73)
A*30	6.8 (22)	4.2 (81)	.60	0.83 (.41–1.66)
A*31	6.8 (22)	5.3 (102)	.27	1.36 (.78–2.38)
A*32	8.0 (26)	8.0 (153)	.35	0.76 (.43–1.34)
A*68	7.7 (25)	7.7 (147)	.79	1.07 (.64–1.80)
B*07	18.2 (58)	26.4 (497)	.27	0.82 (.58–1.16)
B*08	15.1 (48)	27.2 (511)	.13	0.75 (.52–1.08)
B*13	3.1 (10)	3.4 (64)	.68	0.84 (.36–1.93)
B*14	6.3 (20)	8.0 (151)	.28	0.72 (.39–1.31)
B*15	13.2 (42)	15.6 (293)	.79	1.06 (.71–1.56)
B*18	10.4 (33)	6.8 (128)	.74	0.91 (.52–1.60)
B*27	7.2 (23)	8.4 (159)	.78	1.07 (.64–1.79)
B*35	19.8 (63)	11.4 (214)	.62	1.11 (.73–1.69)
B*37	4.4 (14)	2.9 (55)	.09	1.85 (.91–3.74)
B*38	5.7 (18)	1.6 (31)	.97	0.98 (.38–2.53)
B*39	4.7 (15)	3.6 (67)	.55	0.79 (.37–1.70)
B*40	11.9 (38)	13.2 (249)	.56	1.13 (.75–1.70)
B*44	29.9 (95)	31.1 (586)	.28	1.19 (.87–1.62)
B*50	4.4 (14)	1.8 (34)	.02	2.43 (1.14–5.19)
B*51	13.5 (43)	7.9 (148)	.58	1.14 (.71–1.85)
B*55	2.8 (9)	3.8 (71)	.92	0.96 (.43–2.14)
B*57	6.3 (20)	8.6 (162)	.72	0.90 (.52–1.57)
C*01	6.2 (20)	7.5 (120)	.20	0.66 (.35–1.24)
C*02	8.3 (27)	6.7 (107)	.47	1.23 (.70–2.14)
C*03	24.7 (80)	28.5 (456)	.64	1.08 (.78–1.49)
C*04	24.4 (79)	14.4 (230)	.28	1.23 (.84–1.80)
C*05	19.4 (63)	19.9 (318)	.09	1.36 (.95–1.95)
C*06	17.9 (58)	18.5 (296)	.61	1.10 (.76–1.60)
C*07	44.1 (143)	57.9 (928)	.03	0.72 (.54–.97)
C*08	6.5 (21)	8.4 (134)	.22	0.69 (.38–1.26)
C*12	13.9 (45)	7.1 (114)	.76	0.92 (.54–1.57)
C*14	3.4 (11)	1.7 (28)	.59	1.31 (.49–3.50)
C*15	8.3 (27)	3.4 (54)	.10	1.66 (.91–3.02)
C*16	7.4 (24)	8.2 (131)	.71	0.90 (.51–1.58)

ORs were corrected for population stratification. An OR of > 1 reflects protection against HIV infection, and an OR of < 1 reflects susceptibility to HIV infection. None of the variables shown here reached the threshold of significance ($P = .0006$).

Abbreviations: CI, confidence interval; OR, odd ratio.

Table 2. Logistic Regression Analysis Comparing 325 Hemophiliac Human Immunodeficiency Virus–Exposed Seronegative Individuals (Cases) and 1305 Individuals From the 1958 Birth Cohort (Controls) for *KIR* Genes and Genotypic Combination of *KIR* and *HLA*

Test	Cases, % (No.)	Controls, % (No.)	*P* Value	Adjusted OR (95% CI)
KIR2DL1	96.3 (313)	96.9 (1264)	.48	1.37 (.57–3.27)
KIR2DL2	51.7 (168)	50.1 (654)	.89	1.02 (.76–1.37)
KIR2DL3	88.6 (288)	91.7 (1197)	.97	1.01 (.59–1.72)
KIR2DL5	53.2 (173)	46.2 (603)	.27	1.18 (.88–1.59)
KIR2DP1	96.3 (313)	96.9 (1264)	.48	1.37 (.57–3.27)
KIR2DS1	42.2 (137)	36.3 (474)	.09	1.30 (.96–1.76)
KIR2DS2	52.6 (171)	50.6 (660)	.78	1.04 (.78–1.40)
KIR2DS3	31.1 (101)	24.7 (322)	.17	1.26 (.91–1.76)
KIR2DS4	35.4 (115)	39.1 (511)	.84	0.97 (.71–1.32)
KIR2DS5	33.2 (108)	29.7 (388)	.14	1.27 (.93–1.74)
KIR3DL1	96.0 (312)	95.6 (1248)	.49	1.31 (.60–2.85)
KIR3DS1	41.8 (136)	36.2 (473)	.07	1.32 (.98–1.79)
KIR3DS1_hmz	4.0 (13)	4.4 (57)	.49	0.76 (.35–1.66)
HLA-A*3/11	30.8 (100)	35.6 (422)	.19	0.81 (.59–1.11)
HLA-A*3/11 + KIR2DS4	10.5 (34)	14.7 (175)	.08	0.65 (.41–1.06)
HLA*Bw4	66.0 (210)	60.5 (711)	.38	1.15 (.84–1.57)
HLA*Bw4 80I	30.2 (96)	21.9 (258)	.78	0.95 (.66–1.36)
HLA*Bw4 + KIR3DL1	63.2 (201)	58.2 (684)	.31	1.17 (.86–1.60)
HLA*Bw4 80I + KIR3DS1	11.6 (37)	7.7 (91)	.90	0.97 (.55–1.69)
HLA group C1	81.8 (265)	88.7 (758)	.13	0.71 (.46–1.10)
HLA group C1 hmz + KIR2DL3 hmz	16.4 (53)	20.7 (177)	.05	0.65 (.43–.99)
HLA group C2	66.0 (214)	56.0 (479)	.006	1.58 (1.14–2.20)
HLA group C2 hmz + KIR2DL3 hmz	7.7 (25)	5.6 (48)	.75	1.10 (.59–2.06)
HLA group C2 + KIR2DL1	63.6 (206)	53.9 (461)	.002	1.68 (1.21–2.32)
HLA group C2 + KIR2DS1	26.9 (87)	20.0 (171)	.03	1.51 (1.05–2.17)

Only the functional *KIR2DS4* allele was included. ORs were corrected for population stratification. An OR of >1 reflects protection against HIV infection, and an OR of <1 reflects susceptibility to HIV infection. None of the variables shown here reached the threshold of significance ($P = .0006$).

Abbreviations: CI, confidence interval; hmz, homozygous; OR, odd ratio.

in these groups is not easily quantifiable and therefore makes results of the genetic association tests for the risk of infection difficult to interpret. In addition, the risk of infection is estimated to be <1% per exposure in sexual and parenteral contacts, except for cases of contaminated blood transfusion, in which the risk is about 90% (available at: http://www.cdc.gov/hiv/policies/law/risk.html, accessed 17 April 2014). The hemophiliac cohort that we analyzed herein is the most reliable, compared with other HESN cohorts, in terms of the homogenously high risk of infection across participants, detailed clinical data, and the size of the cohort [5]. Several studies suggested a role for *HLA* class I allele and/or *KIR* gene presence or absence in HIV infection in sexual, parenteral, and mother-to-child transmissions [11–13]. These results should be interpreted with caution because of potential shortcomings in terms of samples sizes, exposure quantification, population stratification, and frailty bias, which invariably leads to the enrichment of genotypes that protect against disease progression in cohorts of chronically infected individuals. Nevertheless, the negative data obtained here cannot be readily extrapolated to other types of HIV exposure, owing to potentially distinct mechanisms of protection.

Conversely, HIV transmission between sex partners has been shown to be associated with certain *HLA* class I alleles in the infected partners [14, 15], which is likely due to the influence of these *HLA* class I alleles on viral load. The same studies did not find *HLA* class I allelic associations with resistance to the HIV acquisition in uninfected partners, similar to our findings.

In summary, *HLA* class I and *KIR* genes do not appear to impact HIV acquisition among hemophiliac patients exposed to contaminated blood products. Host genetic factors could still be involved in the resistance phenotype observed in HESN individuals (eg, low-frequency variants poorly tagged by genotyping arrays or structural variants, such as insertion and deletion polymorphisms), and this should be investigated further. Availability of large, randomly selected control groups with available genome-wide genotyping data, such as the 1958 birth cohort, allows a thorough investigation of genetic associations in ethnically matched populations.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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