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***HLA-B* alleles associate consistently with HIV heterosexual transmission, viral load and progression to AIDS, but not susceptibility to infection**

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Abstract

Objective—*HLA* class I polymorphism is known to affect the rate of progression to AIDS after infection with HIV-1. Here we test the consistency of *HLA-B* allelic effects on progression to AIDS, heterosexual HIV transmission and 'setpoint' viral levels.

Methods—We used adjusted Cox proportional hazard models in previously published relative hazard (RH) values for the effect of *HLA-B* alleles on progression to AIDS (n=1089). The transmission study included 303 HIV-1-infected men with hemophilia and their 323 female sex partners (MHCS cohort). Among 259 HIV-1 seroconverters (MACS cohort), HIV RNA levels at 'setpoint' were determined in stored plasma samples by a reverse-transcription polymerase chain reaction assay. *HLA-B* genotyping was performed by sequence-specific-oligonucleotide-hybridization and DNA sequencing.

Results—Several *HLA-B* alleles showed consistent associations for AIDS risk, infectivity and 'setpoint' HIV RNA. *HLA-B**35 was associated with more rapid progression to AIDS (RH 1.39; p = 0.008), greater infectivity (OR 3.14; p = 0.002), and higher HIV RNA (p = 0.01), whereas the presence of either *B**27 or *B**57 associated with slower progression to AIDS (*B**27: RH 0.49, p < 0.001; *B**57: RH 0.40, p < 0.0001), less infectivity (OR 0.22 and 0.31, respectively, though not significant) and lower viral levels (p < 0.0001). Importantly, *HLA-B* polymorphism in female partners was not associated with susceptibility to HIV-1 infection.

Conclusion—*HLA-B* polymorphisms that affect the risk of AIDS may also alter HIV-1 infectivity, probably through the common mechanism of viral control, but they do not appear to protect against infection in our cohort.

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Keywords

HIV; AIDS; HLA; viral load; HIV transmission; AIDS progression; MHC diversity

Introduction

Among a dozen or so genes affecting the natural history of human immunodeficiency virus (HIV infection), *HLA* class I shows the strongest association with progression to acquired immunodeficiency syndrome (AIDS) [1-3]. In response to HIV infection, *HLA* class I molecules play important roles in both T-cell mediated adaptive immunity and natural killer (NK) cell mediated innate immunity. Individual *HLA* class I may influence AIDS pathogenesis by binding and presenting immuno-dominant HIV epitopes to T cells and/or interacting with killer immunoglobulin-like receptors (KIR) to regulate NK cell activity[4,5]. In particular, the *HLA-B*35Px* alleles (a group of *B*35* and *B*53* subtypes encoding molecules that share similar peptide binding characteristics, mainly comprised of *B*3502*, *B*3503*, and *B*5301* in our cohorts[6]) associate with rapid progression to AIDS. *B*27* and *B*57* have been consistently associated with reduced rate of progression to AIDS in multiple epidemiological studies [7]. However, effects of *HLA* on HIV transmission are relatively poorly defined, though the influence of specific *HLA* alleles or shared *HLA* alleles [8,9] on risk of mother to infant HIV transmission [10,11] have been reported. *HLA* influence on heterosexual HIV transmission has also been reported in a Zambian cohort [12].

We recently showed that alleles encoding the HLA-Bw4 and Bw6 epitopes of the HLA-B molecules are associated with risk for HIV transmission in heterosexual couples[13]. The presence of HLA-Bw4 in HIV-1-infected men was associated with a decreased risk of male-to-female HIV-1 transmission, perhaps because HLA-Bw4 allotypes serve as ligands for KIR3DL1 expressed on NK cells. In the present report, we further investigated individual *HLA-B* alleles for their contributions to the risk of HIV-1 transmission from HIV-infected men to their female partners (“infectivity”). We also examined the effect of these alleles on setpoint HIV RNA levels in HIV seroconverters. These data allowed us to compare the pattern of *HLA* associations with AIDS progression, HIV-1 transmission, and HIV-1 viral loads in an attempt to examine potential connections among these associations.

Methods

Study subjects

The subjects for the analysis of HIV transmission were participants in the Multicenter Hemophilia Cohort Study (MHCS), a prospective study of patients with hemophilia and their female partners enrolled at hemophilia treatment sites in the United States and Europe [14]. Between 1986 and 1998, MHCS investigators enrolled women who had had vaginal intercourse with an MHCS participant into a study of heterosexual HIV-1 transmission. At enrollment, the female partner completed a standardized self-administered questionnaire that included questions about HIV-1 exposure and sexual practices. Blood samples were collected for HIV-1 testing. Women were invited for follow-up visits at 6 month intervals for HIV-1-testing and to complete additional questionnaires. The present study includes 303 HIV-infected men with hemophilia and their 323 female partners, of whom 43 (13.3%) had become infected with HIV-1[13]. Twenty men had two partners (2 of the forty partners became infected).

To examine the effect of *HLA* alleles on HIV-1 RNA ‘setpoint’, 259 white men from the Multicenter AIDS Cohort Studies (MACS) were typed for *HLA* class I. These participants

were 'seroconverters' whose estimated date of seroconversion was based on a negative result for antibody to HIV followed by a positive result within an average of 18 months. The effect of *HLA* on transmission and viral load setpoint were compared to previously published survival analyses in which the influence of *HLA* on progression to AIDS1987 was determined in seroconverters [6,7].

Viral assays and HIV-1 RNA set point

The measurement of HIV-1 RNA levels for MACS participants has been described previously[15]. HIV-1 RNA was quantified in stored plasma samples by the Amplicor RT-PCR assay (Roche Diagnostic Corporation, Indianapolis, Ind.), which has a lower detection limit of 400 copies/ml. Measurements between 12 and 24.5 months after seroconversion were used to calculate the set point value, excluding any measures after combination antiretroviral therapy was begun. The HIV-1 RNA measure from the first positive visit was also excluded if it fell within this 12-24.5 month period. The set point was then calculated as the mean of all HIV-1 RNA measures. Only patients with two or more measures were included in the present analysis.

HLA typing

High-resolution (4-digit) *HLA* typing was carried out using sequence-specific-oligonucleotide (SSO) hybridization as described previously[6,7]. Genomic DNA was amplified using locus-specific primers flanking exons 2 and 3 of the class I *HLA* genes. The PCR products were fixed on nucleic acid transfer membranes and hybridized with sequence-specific oligonucleotide (SSO) probes matching polymorphic nucleotide motifs of all known *HLA* alleles. Alleles and genotypes were assigned by SSO hybridization patterns. Ambiguous typing results were resolved by sequencing analysis of exons 2 and 3. High-resolution (4-digit) class I typing was informative for 303 hemophilic men and 276 female partners. Data analyses were performed for 4-digit and 2-digit alleles separately. Except for the *B*35Px/PY* allele groups, data analyses shown in this report were based on 2-digit alleles. *B*35Px* alleles are defined as *B*3502*, *3503*, *3504* and *5301*, and *B*35PY* alleles are defined as *B*3501* and *3508*.

Statistical analysis

In the analysis of HIV transmission, the effect of *HLA* alleles on male HIV-1 infectivity and female partner susceptibility was evaluated in two-by-two tables using Fisher's exact test (Proc FREQ, SAS 9.1, The SAS Institute, Cary, NC, USA) and with logistic regression by calculating adjusted odds ratios (aOR) and 95% confidence intervals (CI), adjusted for race in two categories (white/non-white) and for age of the male partner at estimated date of seroconversion. The effect of the HIV-infected male's *HLA* types on transmission was therefore tested using a total of 323 pairs, where the 283 men who had one female partner were each counted once in the analysis and the 20 men having two partners were each counted twice (data shown in tables). We also performed the analyses with only one randomly selected partner for patients with two partners and the results remained the same (data not shown in tables). To evaluate the influence of racial background on clinical outcomes, all analyses were performed separately with whites only and with all racial groups combined. Non-white groups were too small to be analyzed separately.

For *HLA* associations with HIV RNA levels in MACS seroconverters, t-tests were used to examine the difference of mean viral load between those carrying a particular allele and those who did not carry that allele. We also analyzed the viral load data using linear regression models that adjusted for age in five-year categories.

Results

The demographic information for the MHCS participants is summarized in Table 1. The median age at the estimated date of HIV-1 seroconversion was 26 years for men and 24 years for women. Caucasians accounted for 85.5% of men and 82.3% of women.

The effect of *HLA* on HIV-1 transmission could be examined in 323 couples (323 female partners of 303 HIV-infected men with hemophilia). HIV-1 transmission occurred in 43 of these 323 pairs (13.3%). The results for all subjects are presented in Tables 2 and 3, but similar results were found when the analysis was restricted to whites only (not shown). Table 2 shows the effect of 2-digit *HLA-B* alleles present in the HIV-positive hemophiliacs on HIV-1 transmission to their female partners after adjustment for race and age. Only *B*35*, which was the second most frequent allele, showed a significantly different distribution between the men who transmitted HIV compared to those who did not (aOR 3.14; $p = 0.002$). *B*27* and *B*57*, the two protective alleles, were each detected only once in the transmitting group, resulting in two of the lowest ORs (0.22 and 0.31, respectively), although neither was statistically significant.

The alleles that had previously been associated with AIDS progression (*HLA B*35*, *B*53*, *B*27* and *B*57*) were examined for consistency of their effects on AIDS progression, HIV-1 infectivity, and HIV-1 RNA levels (Table 3). Individuals with *B*35* progressed to AIDS more rapidly (RH 1.39; $p = 0.008$), had higher risk of infectivity among men with hemophilia (aOR 3.14; $p = 0.002$), and had a higher mean HIV RNA set point compared to those without this allele (4.61 HIV RNA $\log_{10}$ copies/ml vs. 4.32 HIV RNA $\log_{10}$ copies/ml, respectively; $p = 0.01$). The *B*35Px* subgroup associated with more rapid progression to AIDS (RH 1.92; $p < 0.0001$), showed the highest risk for HIV-1 transmission (aOR 3.5; $p = 0.007$), and had a significantly higher mean HIV RNA set point, as compared to all others (4.63 vs. 4.36 HIV RNA $\log_{10}$ copies/ml, respectively; $p = 0.04$). The *B*35PY* subgroup was not significantly associated with rapid progression to AIDS (RH 1.12; $p = 0.45$), increased infectivity (aOR 2.04; $p = 0.09$) or higher HIV RNA ($p = 0.07$). *HLA-B*53* (RH = 1.85; $p = 0.004$) was not significantly associated with greater infectivity or higher mean HIV RNA, though both analyses tended towards susceptibility. *B*53* is a common allele in people of African descent, but has a low frequency in Europeans. Since our transmission cohort is primarily composed of European Americans, it is not surprising that any effect of *B*53* did not reach significance.

Individually, both *B*27* and *B*57* had very low aORs (0.22 and 0.31, respectively) for HIV-1 infectivity among hemophiliac men, even though neither allele reached statistical significance due to probably small numbers.

The potential effect of *HLA-B* on susceptibility to HIV-1 infection in female partners was evaluated in 276 women (39 HIV-1-infected and 237 HIV-1-uninfected) who were successfully genotyped for *HLA-B*. No alleles showed a significant association with HIV-1 susceptibility (data not shown), including the *HLA-B* genotypes that are either deleterious or beneficial for progression to AIDS, infectivity, or HIV RNA setpoint (Table 4).

Discussion

Diversity in the *MHC* has been identified as the most significant AIDS-regulating genetic factor [3]. Well-documented evidence has indicated that *HLA* class I polymorphism specifically plays an important role in varied outcomes across individuals following HIV-1 infection [2]. However, analyses based on general populations comparing HIV- to HIV+ individuals have shown little consistent evidence of *HLA* association with HIV infection. In general, the identification of appropriate HIV- and HIV+ groups for comparison requires

careful consideration, as the available groups have great potential for selection biases that may erroneously result in significant differences between the two groups. For example, the loss of rapid progressors amongst HIV+ individuals, which is common across cohorts, may artificially result in a high frequency of variants that associate with longer term nonprogression. Analyses of sero-discordant sexual partners examine both viral transmitters and recipients, providing a better-controlled research design for examining the potential influence of *HLA* class I on HIV-1 transmission and susceptibility to infection.

We recently reported that *HLA-Bw4* was associated with a lower risk for HIV-1 transmission from hemophiliac patients to their female partners [13]. The two low-risk alleles for HIV-1 transmission, *B*27* and *B*57*, that we detected in the present study both belong to the Bw4 antigen group. The Bw4 epitope on the alpha-1 domain of the class I *HLA* molecule forms part of the F-pocket that accommodates the C-terminal anchor residue of the bound peptide. This complex is recognized by the natural killer cell receptor KIR3DL1, which may explain the general protection of the group of alleles containing the Bw4 epitope. In addition, *B*27* and *B*57* are known to have characteristics that can delay HIV-1 adaptation to the host MHC [16-18], explaining in part why these two alleles exhibit the strongest protective effect on AIDS progression, as well as HIV transmission, relative to all other Bw4 bearing *HLA-B* alleles.

HIV-1 transmitters (men with hemophilia) and recipients (their female partners) showed different patterns of *HLA* associations. In the men, *B*35* (especially *B*35Px*, though *B*35PY* also tended in the same direction) was detected as a high-risk allele for HIV-1 transmission, whereas *B*27* and *B*57* were associated with low risk. In female partners, none of the previously detected AIDS-regulating *HLA* alleles showed an association with susceptibility to HIV-1 infection, consistent with a model in which *HLA* class I diversity affects outcome after HIV infection, but not infection itself. While our sample size was small, there were no consistent tendencies for effects of these alleles on infection with those observed for viral load control, AIDS progression, and transmission. Our study was largely composed of European Americans infected with clade B virus, such that our results pertain to this ethnic group. Nevertheless, our data concur with a recent report showing that *HLA* alleles/haplotypes associated with transmission in an African cohort do not associate with acquisition in their heterosexual partners [12]. The different patterns of genetic associations illustrate that HIV-1 transmission and susceptibility to infection involve different host/viral mechanisms and therefore are subject to different genetic influences.

Our null data on susceptibility of heterosexual acquisition of HIV-1 infection among women are also consistent with a study on *HLA* and mother-to-infant HIV-1 transmission in which the *HLA-B* genotype of the recipient (the infant) did not alter the risk of transmission, whereas the *HLA-B* genotype of the HIV transmitter (the mother) was associated with varied risks for HIV-1 transmission [9]. If there is indeed an effect of *HLA* polymorphism on susceptibility to HIV-1 infection, it may very well differ from that for viral transmission. For example, *MHC* polymorphism might affect susceptibility by influencing innate immunity against HIV-1 infection through specific interactions with KIR. A larger sample with more HIV-1 infected women is needed to test this hypothesis.

*B*35* showed consistent, significant associations with AIDS progression, HIV transmission, and HIV viral load levels, suggesting that the molecular variation of *B*35* impacts these related processes in a coherent manner. While these associations appeared to be driven primarily by *B*35Px* for both progression to AIDS and HIV infectivity, lack of viral load control was observed for both *B*35Px* and *B*35PY*. Thus, both subgroups of *B*35* may confer some level of susceptibility, especially in terms of viral load control, though *B*35Px* appears to have a stronger effect on AIDS progression and infectivity.

The consistent effects of *B*35Px*, *B*27* and *B*57* on AIDS progression and transmission suggest that *HLA* polymorphism may influence these events through a common mechanism. A likely explanation is the control of HIV viremia. In support of this model, the high risk *B*35Px* was associated with higher setpoint HIV RNA levels, an indicator of more rapid AIDS progression [19,20], while the two protective alleles *B*27* and *B*57* were associated with lower setpoint HIV RNA levels. Furthermore, an association between HIV RNA level in blood and heterosexual transmission has been reported previously [21], as has faster progression to AIDS with higher likelihood of heterosexual transmission [22,23]. Our analysis suggests that *HLA* class I polymorphisms contribute to these relationships.

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Table 1

Characteristics of 303 HIV-1-infected men with hemophilia and their 323 female partners.

Characteristic	Number (Median)	% (IQR)
Age (at estimated date of seroconversion of man)		
Men (n=303)	(26)	(19-34)
Women (n=323)	(24)	(17-31)
Race		
Men (n=303)		
White	259	85.5%
Black	24	7.9%
Hispanic	17	5.6%
American Indian or Alaskan native	3	1.0%
Women (n=323)		
White	266	82.4%
Black	31	9.6%
Hispanic	21	6.5%
Asian of Pacific Islander	3	0.9%
American Indian or Alaskan native	2	0.6%
Start of sexual relationship (n=289)		
Before HIV-1 seroconversion of man	111	39.8%
After HIV-1 seroconversion of man	168	60.2%

IQR, interquartile range (25th and 75th percentiles)

Table 2Effect of *HLA-B* alleles (2-digit) on HIV transmission from HIV-infected men with hemophilia to their female partners

HLA	NT (280)	T (43)	OR*	95% CI	P-value
B*07	52	4	0.53	0.05 - 1.58	0.26
B*08	60	10	1.29	0.59 - 2.85	0.53
B*13	21	2	0.63	0.14 - 2.88	0.56
B*14	22	5	1.64	0.57 - 4.72	0.36
B*15	38	2	0.24	0.05 - 1.06	0.06
B*18	30	3	0.64	0.18 - 2.23	0.48
B*27	27	1	0.22	0.03 - 1.68	0.14
B*35	43	16	3.14	1.53 - 6.48	0.002
B*37	3	1	5.54	0.49 - 62.06	0.17
B*38	26	1	0.22	0.03 - 1.68	0.14
B*39	8	3	2.50	0.60 - 10.48	0.21
B*40	27	3	0.68	0.19 - 2.42	0.55
B*41	6	1	1.04	0.12 - 9.26	0.97
B*42	4	1	0.81	0.08 - 8.10	0.93
B*44	64	8	0.85	0.37 - 1.97	0.71
B*45	5	3	3.64	0.79 - 16.70	0.09
B*48	1	0			
B*49	11	0	-		
B*50	5	1	1.06	0.12 - 9.71	0.96
B*51	28	4	1.32	0.42 - 4.13	0.64
B*52	5	0	-		
B*53	7	3	1.72	0.39 - 7.53	0.47
B*55	10	1	0.64	0.08 - 5.15	0.68
B*56	4	0	-		
B*57	20	1	0.31	0.04 - 2.39	0.26
B*58	5	4	3.85	0.90 - 16.45	0.07
B*78	1	0			
B*81	0	1			

T: HIV transmitting male

HLA-B alleles that are deleterious or beneficial for AIDS risk, infectivity, and HIV RNA setpoint

Table 3

Outcome	AIDS Risk			HIV Infectivity			HIV RNA Set Point				
Subjects	HIV Seroconverters [7]	Men with Hemophilia (MHCS)		HIV Seroconverters (MACS)							
	N = 1089	N=43	N=280	N = 259							
	T		NT	Present		Absent					
HLA Allele	n	RH	p	n (%)	OR*	p	n	Mean	p		
<i>Deleterious</i>											
B*35 (Bw6)	171	1.39	0.008	16(37.2)	43(15.4)	3.14	0.002	46	4.61	4.32	0.01
B*53 (Bw4)	82	1.85	0.004	3 (7.0)	7 (2.5)	1.72	0.47	7	4.62	4.38	0.33
B*35Px (Bw4,6)	140	1.92	<0.0001	9 (20.9)	18 (6.4)	3.5	0.007	29	4.63	4.36	0.04
B*35PY (Bw6)	119	1.12	0.45	10(23.3)	32(11.4)	2.04	0.09	25	4.60	4.34	0.07
<i>Beneficial</i>											
B*27 (Bw4)	83	0.49	0.001	1 (2.3)	27(9.6)	0.22	0.14	21	3.93	4.44	0.001
B*57 (Bw4)	57	0.40	<0.0001	1 (2.3)	20 (7.1)	0.31	0.26	20	3.87	4.43	0.0003

T: HIV transmitting male
NT: HIV non-transmitting male
* Adjusted for race and age

Table 4

Frequency of deleterious or beneficial *HLA-B* alleles among HIV-infected and HIV-uninfected female sex partners of HIV infected men with hemophilia

HLA allele	Female sex partners		OR	p
	HIV- N=237	HIV+ N=39		
	n (%)	n (%)		
<i>Deleterious</i>				
B*35 (Bw6)	41 (17.3)	6 (15.4)	0.84	0.72
B*53 (Bw4)	8 (3.4)	3 (7.7)	1.03	0.97
B*35Px (Bw4,6)	21 (8.9)	6 (15.4)	1.33	0.58
B*35PY (Bw6)	30 (12.7)	4 (10.3)	0.71	0.56
<i>Beneficial</i>				
B*27 (Bw4)	13 (5.5)	0	-	-
B*57 (Bw4)	13 (5.5)	2 (5.1)	1.14	0.87