

Host Genetic Profiles Strongly Correlate with Virologic and Immunologic Outcomes in HIV-1 Seroprevalent and Primarily African-American Adolescents

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Background: HIV-1 pathogenesis can be regulated by genetic variations at several loci involved in natural and acquired immunity. We evaluated the correlation between host genetic profiles (defined by HLA and HIV-1 coreceptor variants) and the virologic and immunologic outcomes among HIV-1-infected adolescents from the Reaching for Excellence in Adolescent Care and Health (REACH) cohort.

Methods: 227 HIV-1 seropositive REACH adolescents (ages 13-18, 75% females, and 71% African-Americans) with quarterly follow-up visits (1996-2000) were categorized into three groups based on average plasma HIV-1 RNA concentration {viral load (VL) in copies per mL} and CD4⁺ T-cell counts (cells per mL) during a 6-12 months interval when antiretroviral therapy (ART) was not taken. HLA class I and HIV-1 coreceptor (CCR) alleles and haplotypes were resolved using molecular techniques including PCR-SSP, reference-strand conformation analysis, and DNA sequencing. Each HLA and CCR variant with a previously reported risk and protective effect on HIV-1 pathogenesis was assigned a score of -1 and +1, respectively. Individuals with identical net scores were grouped and analyzed in relation to VL and CD4⁺ cell counts.

Multivariable models were applied to assess the relative effects of genetic scores along with other host variables including race, gender, and prior exposure to ART.

Results: Adolescents (n=40) with a clearly favorable combination of VL (<1,000) and CD4 counts (>450) consistently had more positive (+1 to +2) than negative (-1 to -4) scores compared with those (n=80) with an unfavorable combination (VL >16,000 and CD4 <450) or the remainder (n=107) of the cohort (p<0.0001). Close association of genetic profile with mean log₁₀ VL remained persistent (p<0.0001) after adjustment for differences in gender (p = 0.048), race (p = 0.721), and history of ART (p = 0.001).

Conclusions: HLA and CCR genotyping data can offer another tool for predicting clinical outcomes. The prognostic value of our genetic scoring algorithm (GSA) in both clinical and investigative settings will undoubtedly improve as effects of additional host genetic factors are revealed and confirmed.

TABLE 1. Distribution of genetic (HLA class I and CCR) markers in 227 HIV-1 seropositive and 183 seronegative REACH participants.

Genetic markers	Score	AAs		Others		Combined	
		HIV-1+ (n = 161)	HIV-1- (n = 117)	HIV-1+ (n = 66)	HIV-1- (n = 66)	HIV-1+ (n = 227)	HIV-1- (n = 183)
HLA class I markers							
B*27	+1	5 (4.3) ^b	3 (2.6) ^b	1 (1.5) ^b	8 (12.1) ^b	6 (2.6) ^b	11 (6.0) ^b
B*35	-1	23 (19.6)	17 (14.5)	11 (13.6)	16 (24.2)	34 (14.9)	33 (18.0)
B*53	-1	45 (21.6)	40 (34.2)	4 (6.1)	6 (9.0)	49 (21.6)	46 (25.1)
B*57	+1	13 (7.5)	6 (5.1)	4 (6.1)	5 (7.5)	17 (7.5)	11 (4.4)
Hmz ^c at all three loci	-3	0	2 (1.1)	1 (1.5)	1 (1.5)	1 (0.4)	3 (1.6)
Hmz ^c at two loci	-2	2 (1.2)	8 (4.4)	2 (3.0)	3 (4.5)	4 (1.8)	11 (6.0)
Hmz ^c at a single locus	-1	22 (13.6)	29 (15.8)	10 (15.1)	9 (13.6)	32 (14.1)	38 (20.8)
CCR2-CCR5 markers^d							
HHG*2 (=Δ32)	+1	7 (4.4)	3 (2.6)	3 (4.5)	1 (1.5)	10 (4.4)	4 (2.1)
HHF*2 (=64I)/G*2	+1	1 (0.4)	0	0	0	1 (0.4)	0
HHE/E	-1	5 (3.9)	2 (2.2)	4 (6.1)	4 (6.1)	9 (3.9)	6 (3.2)

^a Individual HLA class I factors identified in multiple cohort studies [1-4].

^b Numbers correspond to n (%).

^c Hmz, homozygosity = identical 4-digit alleles detected at each locus.

^d Also reported in multiple cohorts [5-8].

TABLE 2. Association of individual genetic (HLA class I and CCR) markers with HIV-1 RNA concentration in 207 HIV-1 seropositive AIDS-free REACH participants.

Genetic markers	HIV-1 VL ^a (Mean ± SD)	Univariate GLM p ^b	Adjusted ^c univariate GLM p ^c
HLA class I markers^d			
B*27 (n = 6)	3.53 ± 0.49	0.6902	0.6500
B*35 (n = 31)	3.98 ± 0.61	0.0599	0.0528
B*53 (n = 45)	3.89 ± 0.71	0.0893	0.1093
B*57 (n = 17)	2.34 ± 1.04	<0.0001	<0.0001
Hmz ^e at any locus (n = 33)	3.89 ± 0.83	0.5307	0.3298
CCR2-CCR5 markers^f			
HHG*2 (=Δ32) (n = 10)	3.69 ± 0.52	0.9742	0.7473
HHF*2 (=64I)/G*2 (n = 1)	3.64	0.9629	0.9895
HHE/E (n = 9)	4.08 ± 0.99	0.1704	0.0571

^a HIV VL = viral load (HIV-1 RNA concentration); overall mean = 3.62 ± 1.03 log₁₀ in the 207 AIDS-free participants.

^b General linear regression model (GLM) analyses for subjects with and without a specific marker.

^c Adjusted for race, gender, age, and patient groups based on number of follow-up visits and treatment history.

^d Individual HLA class I factors identified in multiple cohort studies [1-4].

^e Hmz, homozygosity = identical 4-digit alleles detected at each locus.

^f Also based on multiple cohorts [5-8].

Summary

1. A genetic scoring algorithm (GSA) was applied to sum up multiple HLA and CCR2-CCR5 markers in each individual (Table 1).
2. Subjects with favorable genetic scores showed better virologic and immunologic control of HIV-1 infection compared to those with either a neutral score or negative scores (overall p<0.0001 after adjustment for race, gender, age, and prior exposure to antiretroviral therapy (Table 3)).
3. In AIDS-free adolescents, each unit increment in genetic score was associated with 0.28 log₁₀ copies per mL of plasma viral load (adjusted p<0.0001) (Table 5).
4. Genetic scores outperformed individual markers (Tables 2 and 4) in predicting virologic and immunologic outcomes in chronic HIV-1 infection.

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TABLE 3. Differential distribution of genetic scores in 227 REACH adolescents categorized by their HIV-1 viral RNA concentration and CD4⁺ T-cell counts.

Categorical scores ^a	Controllers ^b (n = 37)	Reference Group ^b (n = 134)	Non-controllers ^b (n = 56)
≤-2	0	16 (11.9) ^c	10 (17.9) ^c
-1	4 (10.8)	41 (30.6)	22 (39.3)
0 ^d	21 (56.8)	65 (48.5)	23 (41.1)
≥ +1	12 (32.4)	12 (9.0)	1 (1.8)

^a Z = -5.1, 2-tailed p < 0.0001.

^b Controllers are subjects with favorable outcomes (HIV-1 RNA concentration <1,000 and CD4⁺ cells >450); Non-controllers are those with unfavorable outcomes (HIV-1 RNA concentration >16,000 and CD4⁺ cells <450); Reference group has all seropositive subjects in the remainder of the cohort.

^c Numbers correspond to n (%).

^d All having equal number of positive and negative scores.

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TABLE 4. Distribution of individual genetic (HLA class I and CCR) markers in 227 HIV-1 seropositive REACH participants divided into three categorical degrees of disease control.

	Patient categories with distinct outcomes				
	Cs ^a (n = 37)	Reference group ^a (n = 134)	NCs ^a (n = 56)	p for trend	Adjusted p for trend ^b
B*27 (n = 6)	0	5	1	0.780	-
B*35 (n = 31)	0	22	9	0.012	0.010
B*53 (n = 45)	2	31	12	0.033	0.025
B*57 (n = 17)	12	5	0	<0.0001	<0.0001
Hmz ^c at any locus (n = 33)	3	20	10	0.048	0.110
HHG*2 (=Δ32) (n = 10)	2	8	0	0.137	-
HHF*2 (=64I)/G*2 (n = 1)	0	1	0	-	-
HHE/E (n = 9)	1	5	3	0.502	-

^a Controllers (Cs) and non-controllers (NCs) as defined in Table 3.

^b Adjusted for race, gender, age, and patient groups.

^c Hmz, homozygosity = identical 4-digit alleles detected at each locus.

TABLE 5. Association of genetic (HLA class I and CCR) scores with HIV-1 RNA concentration in 207 AIDS-free REACH participants.

Genetic scores	HIV-1 viral load (Mean ± SD)	Overall, viral load (HIV-1 RNA concentration in plasma) decreases by an average of 0.275 (SD = 0.064) and 0.254 (SD = 0.063) log ₁₀ , respectively, per +1 unit increase in genetic score (p < 0.0001) before and after adjustment for other host variables (age, gender, race, and patient group ^a).
≤-2	4.16 ± 0.56	
-1	3.82 ± 0.81	
0	3.66 ± 0.97	
≥ +1	3.17 ± 0.91	

^a Three groups of patients defined by exposure to antiretroviral therapy and consecutive visits with viral load measurements.

Feedback

Human Major Histocompatibility Complex (HLA) Class I Variants in HIV-1-infected Zambians and Their Relative Effect on Plasma Viral RNA Concentration in the Absence of Antiretroviral Therapy

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Abstract #B126e

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Background: Allelic forms of human major histocompatibility complex (HLA) class I molecules differentially present endogenous antigens to CD8⁺ cytotoxic T-lymphocytes (CTLs) for immune surveillance. The impact of HLA alleles on HIV-1 disease progression has often differed in the magnitude and consistency across cohorts, ethnicity, and various stages of infection. Among relatively healthy seroconverted and seroprevalent participants in the Zambia-UAB HIV Research Project, we examined the relative contribution of HLA class I alleles to the variability in HIV viral load (VL), which predicts both disease progression and sexual transmission.

Methods: HLA class I alleles in 259 HIV-1 clade C virus-infected Zambians (137 females and 122 males) were resolved by molecular techniques including PCR with sequence-specific primers, reference-strand conformation analysis, and DNA sequencing. The distributions of major HLA alleles and haplotypes (carrier frequency $\geq 2\%$) were compared among participants categorized according to their plasma HIV-1 RNA concentration. The relative HLA effects on mean log₁₀ VL were assessed by multivariable analytic techniques.

Results: HIV VL was lower in HLA B*39-, B*5703-, and A*30-Cw*03-carriers ($p = 0.001-0.003$) and higher in those carrying B*18, B*41, B*45, and A*29-B*42 ($p = 0.01-0.09$). These effects persisted with adjustment for age, gender, and duration of infection. In contrast, neither B*35 ($n=15$) nor B*53 ($n=53$) showed any of the disadvantage reported elsewhere for those alleles.

Associations of additional alleles (A*68, Cw*12, Cw*16, and Cw*18) with unusually high or low VL ($p = 0.0003-0.04$) were largely due to their tight linkage disequilibria with HLA-B variants. Overall, the three most favorable HLA class I variants were found in 31% of subjects with VL <1,000 and 3% of those with VL > 100,000.

Conclusion: HLA class I alleles and haplotypes that influence HIV-1 VL in clade C virus-infected Zambians appeared rather dissimilar to those seen earlier in clade B virus-infected Caucasians. In successive generations of clade C HIV-1-infected populations, diminished frequency of unfavorable and concomitant accumulation of favorable HLA class I variants can alter the genetic composition of HIV/AIDS vaccine target groups.

Table 1. Major HLA class I haplotypes observed in Zambians (2N = 762).

Haplotypes ^a	Frequency ^b	Presence in other ethnic groups ^c
A*01-Cw*18-B*8101	10 (0.013)	No
A*02-Cw*02-B*15	19 (0.025)	No
A*02-Cw*07-B*07	8 (0.010)	AA, C, H, & NAN
A*02-Cw*16-B*45	15 (0.020)	AA
A*02-Cw*16-B*58	4 (0.005)	No
A*23-Cw*02-B*15	18 (0.024)	No
A*23-Cw*04-B*53	11 (0.014)	No
A*23-Cw*08-B*14	13 (0.017)	No
A*23-Cw*07-B*07	16 (0.021)	AA
A*23-Cw*16-B*45	11 (0.014)	No
A*30-Cw*03-B*15	17 (0.022)	No
A*30-Cw*04-B*53	28 (0.037)	No
A*30-Cw*07-B*08	14 (0.018)	No
A*30-Cw*08-B*14	22 (0.029)	No
A*30-Cw*17-B*42	40 (0.052)	No
A*30-Cw*18-B*57031	20 (0.026)	No
A*34-Cw*04-B*44	8 (0.010)	No
A*3601-Cw*02-B*15	8 (0.010)	No
A*66-Cw*06-B*58	13 (0.017)	No
A*68-Cw*03-B*15	16 (0.021)	No
A*68-Cw*07-B*07	19 (0.025)	No
A*68-Cw*08-B*14	19 (0.025)	No
A*68-Cw*16-B*45	10 (0.013)	No
A*74-Cw*02-B*15	16 (0.021)	No
A*74-Cw*04-B*35	9 (0.012)	No
Combined	380 (0.499)	-

^a Likelihood ratio (LR) ≥ 2.0 , $p \leq 0.01$ in all pair-wise 2x2 contingency tables.

^b The actual haplotype frequency {n (%)} can be lower than the observed.

^c Five US populations (n = 187-358) [1] (AA, African-Americans; C, Caucasians; H, Hispanics; NAN, North American Natives) and Rwandans (n = 280) [2].

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Summary

- HLA class I haplotypes are unique in Zambians compared those documented for other racial/ethnic groups (Table 1).
- Low viral load (RNA concentration in the plasma) in HLA-B*57 positive individuals (Tables 2-3) was highly consistent with delayed disease progression (time to AIDS) observed earlier in multiple cohorts in the US and Rwanda (Refs. 3-6).
- Three unfavorable and four favorable HLA class I alleles and haplotypes showed stable association with variability in viral load (Table 3).
- B*35 and B*53 had no appreciable impact on HIV-1 viral load in the ZUHRP cohort (Table 4).

Table 2. HLA variants associated with HIV-1 RNA level as a categorical variable.

HLA variants ($\geq 2\%$)	Plasma HIV-1 RNA (copies per mL)			p value		
	n	<10,000 (n = 55)	10k-100k (n = 106)	>100,000 (n = 98)	Unadjusted	Adjusted ^a
A*02-Cw*16	15	1	5	9	0.051	0.008
A*02-B*45-Cw*16	11	1	4	6	0.193	0.040
A*23-B*14	12	1	4	7	0.115	0.031
A*23-Cw*08 ^b	12	1	5	6	0.237	0.106
A*23-Cw*08-B*14 ^b	10	1	4	5	0.316	0.192
A*23-Cw*07	18	1	6	11	0.023	0.084
A*29-B*42	11	3	7	1	0.117	0.019
A*30-B*57	11	5	6	0	0.005	0.001
A*30-Cw*18-B*57	9	3	6	0	0.043	0.011
A*30-Cw*03	12	5	6	1	0.018	0.008
A*30-Cw*03-B*15	8	4	3	1	0.039	0.012
A*3601 ^b	41	4	20	17	0.161	0.163
A*68	74	12	28	34	0.076	0.087
A*74-B*15 ^b	12	4	6	2	0.116	0.142
B*13 ^b	10	4	4	2	0.116	0.129
B*18	14	0	7	7	0.088	0.060
B*39	9	6	2	1	0.003	0.012
B*39-Cw*12	8	5	2	1	0.011	0.025
B*41	7	0	2	5	0.050	0.019
B*45	44	3	19	22	0.010	0.011
B*45-Cw*16	26	1	11	14	0.017	0.020
B*57	18	8	9	1	0.001	0.001
B*57-Cw*18	15	6	9	0	0.003	0.002
Cw*12	8	5	2	1	0.011	0.025
Cw*16	41	4	17	20	0.037	0.037
Cw*18	32	14	13	5	0.0003	0.0003
Cw*18, no B*57	17	8	4	5	0.052	0.067
All favorable HLA ^c	37	17	17	3	<0.0001	<0.0001
Unfavorable HLA ^c	43	3	15	25	0.004	0.0005

^a Adjusted for age, sex, and patient-group membership (transmission pair donors, transmission pair seroconverters, and discordant pair seropositives).

^b Became marginally significant in subsequent analyses (Table 3).

^c Favorable (A*30-Cw*03, B*39, and B*57) and unfavorable (A*02-Cw*16 and A*23-B*14, and A*23-Cw*07) variants showed stable associations with viral load levels in both categorical and general linear model statistics.

Table 4. Reduced multivariable models summarizing the contributions of HLA class I and non-genetic host factors to variation in HIV-1 RNA level.

	GLM p in model 1 ^a	GLM p in model 2 ^b
Age (per year)	0.004	0.004
Sex (F vs. M)	0.142	0.152
Patient groups ^c	0.0005	0.0005
HLA markers	-	-
Favorable HLA ^d (n = 37)	<0.0001	<0.0001
Unfavorable HLA ^d (n = 43)	0.001	0.001
B*35 (n = 17)	0.745	na ^e
B*53 (n = 58)	0.404	na ^e

^a Based on the univariate analyses (except for B*35 and B*53) shown in Tables 2-3.

^b Based on all markers with an adjusted $p \leq 0.05$ in multivariable analyses.

^c Patient-group membership (transmission pair donors, transmission pair seroconverters, and discordant pair seropositives).

^d Favorable (A*30-Cw*03, B*39, and B*57) and unfavorable (A*02-Cw*16 and A*23-B*14, and A*23-Cw*07) variants showed stable associations with viral load levels in both categorical and general linear model statistics (Tables 2-3).

^e na, not applicable: dropped out of the final model ($p > 0.05$).

Table 3. HLA variants associated with HIV-1 RNA level as a continuous variable.

HLA variants ($\geq 2\%$)	n	Log ₁₀ VL	Unadjusted	Adjusted ^a
		Mean \pm SD	GLM p	GLM p
A*02-Cw*16	15	4.997 \pm 0.769	0.010	0.025
A*02-Cw*16-B*45	11	4.951 \pm 0.870	0.230	0.081
A*23-B*14	12	5.143 \pm 0.608	0.033	0.009
A*23-Cw*08	12	5.070 \pm 0.576	0.072	0.030
A*23-Cw*08-B*14	10	5.053 \pm 0.621	0.118	0.078
A*23-Cw*07	18	5.106 \pm 0.540	0.015	0.075
A*29-B*42	11	4.398 \pm 0.704	0.234	0.094
A*30-B*57	11	4.089 \pm 0.603	0.011	0.004
A*30-Cw*18-B*57	9	4.196 \pm 0.595	0.062	0.025
A*30-Cw*03	12	4.143 \pm 0.738	0.016	0.017
A*30-Cw*03-B*15	8	4.105 \pm 0.710	0.036	0.018
A*3601	41	4.881 \pm 0.677	0.065	0.042
A*68	74	4.836 \pm 0.727	0.034	0.022
A*74-B*15	12	4.298 \pm 0.877	0.088	0.076
B*13	10	4.038 \pm 1.026	0.009	0.019
B*18	14	4.986 \pm 0.436	0.125	0.069
B*39	9	3.891 \pm 0.960	0.002	0.010
B*39-Cw*12	8	3.995 \pm 0.838	0.012	0.039
B*41	7	5.052 \pm 0.552	0.196	0.166
B*45	44	4.885 \pm 0.649	0.050	0.061
B*45-Cw*16	26	4.957 \pm 0.631	0.051	0.067
B*57	18	4.111 \pm 0.807	0.002	0.0002
B*57-Cw*18	15	4.090 \pm 0.782	0.003	0.0006
Cw*12	8	3.995 \pm 0.970	0.012	0.039
Cw*16	41	4.867 \pm 0.610	0.085	0.059
Cw*18	32	4.276 \pm 0.796	0.002	0.0006
Cw*18, no B*57	17	4.415 \pm 0.794	0.205	0.205
All favorable HLA ^b	37	4.110 \pm 0.799	<0.0001	<0.0001
Unfavorable HLA ^c	43	5.052 \pm 0.625	0.0005	0.0002

^a Adjusted for age, sex, and patient-group membership (transmission pair donors, transmission pair seroconverters, and discordant pair seropositives).

^b Favorable (A*30-Cw*03, B*39, and B*57) and unfavorable (A*02-Cw*16 and A*23-B*14, and A*23-Cw*07) variants showed stable associations with viral load levels in both categorical and general linear model statistics.

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Feedback
