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BRIEF REPORT

Impact of Human Leukocyte Antigen Allele–Killer Cell Immunoglobulin-like Receptor Partners on Sexually Transmitted Human Immunodeficiency Virus Type 1 Infection

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Human leukocyte antigen (HLA) class I/killer cell immunoglobulin-like receptor (KIR) genotypes influence human immunodeficiency virus type 1 (HIV-1) disease progression and viral load, but their role in primary infection is uncertain. Inconsistent results from previous studies suggest that the inoculum size and transmission route—parenteral versus sexual—may influence this association. We conducted a genome-wide association study in a population of people with HIV-1 and HIV-1–exposed seronegative individuals exposed to the virus through the sexual route. Our data do not support any role of the HLA/KIR system in susceptibility to sexually transmitted HIV-1 infection. The genetics basis of HIV-1 viral load and disease progression are distinct from the genetics of HIV resistance, a paradox worth exploring.

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

There is wide variability in the clinical course of human immunodeficiency virus type 1 (HIV-1) infection. The progression from primary infection to AIDS—in the absence of treatment—may take from 2 to 25 years with a mean of 10 years. HIV-1–related phenotypes include elite controllers, long-term nonprogressors, or rapid progressors, who progress to AIDS in a 2- to 4-year period. Additionally, HIV-1–exposed seronegative subjects (HESN) are of particular interest for understanding genetic factors that might influence HIV-1 infection. Homozygous *CCR5* null alleles are the unique validated genetic resistance factor for primary infection in HESN, and heterozygotes are protected against disease progression once the infection is established [1].

Paradoxically, the human leukocyte antigen (HLA) loci and their ligands—killer cell immunoglobulin-like receptors (KIRs)—have been shown to influence disease progression and viral load [2], but their role in resistance to HIV-1 acquisition is uncertain [3–5]. Fellay et al first reported the association of the allele HLA-B*57:01 with low viral load [6]. Furthermore, other alleles from HLA-I loci have been associated with viral load, control of infection, and disease progression as B*27:05 and HLA-B*57:03 [7, 8]. In contrast, HLA-B*35 showed the greatest negative impact on viral load and was correlated with rapid progression to AIDS [8] (Supplementary Figure 1).

The KIRs are a group of 13 highly polymorphic genes coding for ligands of HLA class I (HLA-I) proteins. The number of KIR genes is highly flexible, varying between 7 and 14 in several haplotypes. Nevertheless, a conserved set of 4 genes is present in all the haplotypes (3DL3, 3DP1, 2DL4, and 3DL2) [8]. Inhibitory KIR receptors sense the levels of HLA-I expression on cells—a proxy of infection or stress—and deactivate natural killer cells. On the contrary, activating receptors signal for natural killer cell–mediated lysis of the infected cells [9]. The activating receptors appear to function as an invariant T-cell receptor or pattern-recognition receptor, recognizing HLA-I loaded with highly conserved pathogen-derived proteins [10].

Some KIR genes are associated with an elevated risk of HIV-1 infection; however, the influence of HLA, KIRs, and their combinations on resistance to HIV-1 infection have not been consistent across studies [4, 11]. The inconsistent results may arise from differences in the barriers that the virus encounters in the sexual mucosa versus blood and the viral load of the HIV-1–infected partner as previously hypothesized [4].

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The most robust data about the role of genetic background on the clinical course of infectious diseases in general and HIV-1 in particular comes from genome-wide association studies (GWASs); however, the complexity of the KIR loci has hampered the use of this experimental approach to unveil the contribution of these loci to the sexual transmission of HIV-1. The unique GWAS available testing the HLA-KIR epistatic interaction found no genetic associations with resistance to HIV-1 among HESN persons with hemophilia exposed to blood products [4].

In this study, we investigated the impact of HLA and KIR loci on HIV-1 susceptibility via sexual transmission using newly generated GWAS genotypes. We tested the hypothesis that the interplay between the route of HIV-1 transmission and the size of the inoculum may interact with the complex HLA-KIR system. This premise has been proposed to explain the lack of association between the HLA-KIR system in HESN [4].

METHODS

Study Population

The studied population included previously described cohorts of men who have sex with men (MSM) and heterosexual serodiscordant couples from Spain (Jaén, Córdoba, and Madrid) and Italy (Florence), in whom sexual intercourse was routinely unprotected [12]. Additionally, a cohort of MSM from the United States was also genotyped. These American volunteers participated in a placebo-controlled phase 3 trial of a prophylactic vaccine against HIV-1 infection (Vax004 trial, ClinicalTrials.gov identifier: NCT00002441). The epidemiological, clinical, and main characteristics of these patients have been previously described in detail [12]. Trial volunteers (N = 425) were followed for 1200 days after vaccine or placebo administration, thus providing information on time to seroconversion.

Genotyping, Imputation, and Biostatistics

The genotyping included 863 individuals sexually exposed to HIV-1 who have self-reported European ancestry. Among them, 480 were HIV-1 seropositive and 383 were HESN. Genotyping methods, quality controls, imputation of the HLA and KIR genes, and further details are described in the Supplementary Methods. In brief, Plink software was used to perform the GWAS analysis, adjusted by the 4 main principal components plus age, sex, and vaccine status. Otherwise, for the VAXGEN cohort, Kaplan-Meier estimates of the cumulative probability of HIV-1 infection were calculated using the log-rank test. Only a 2-sided P value $<10^{-8}$ was considered significant. After quality control, the cohort included 709 individuals: 346 were HIV-1 seropositive and 363 were HESN; 119 were women (16.8%) and 590 (83.2%) men; and there were 448 258 SNPs.

Ethics

This study was designed and conducted following the principles of the Helsinki Declaration and received approval from the Institutional Review Board of the Province of Jaén, Junta de Andalucia (protocol number GEN-VIH/0646-N-20). All volunteers provided written informed consent to participate in this study.

RESULTS

Genotype imputation was possible for 596 samples for HLA-A, 636 for HLA-B, 593 for HLA-C, and 709 for KIR genes. Frequencies of the HLA-I alleles were compared between HESN and people with HIV (PWH) (Table 1). After multiple testing correction, none of the HLA-A and HLA-C alleles showed differences in allelic distribution between cases and controls nor was the rate of HIV-1 seroconversion significantly influenced by the HLA genotypes, calculated using the Kaplan-Meier method and analyzed by the log-rank test. When testing HLA-B allele distribution, B*51 showed the lowest nominal P value (9.4% vs 5.4%; odds ratio [OR], 1.82 [95% confidence interval {CI}, 1.2–2.9]; $P = .0093$; adjusted $P = .56$). This allele did not show an impact on time to HIV-1 seroconversion (log-rank test $P = .1$; adjusted $P = 1$) (Table 1). Similarly, KIR gene frequencies as well as number of copies were compared between HESN and PWH; no significant differences were observed in any case (Table 2).

Finally, we conducted additional testing to explore paired receptor-ligand epistatic interactions comparing PWH and HESN; none of the results exhibited statistical significance (Supplementary Table 1).

DISCUSSION

HLA class I alleles A*01, C*06:02, and C*07:01 were previously found significantly enriched in HESN women exposed to HIV-1 by the sexual route. Furthermore, women carrying these alleles seroconverted significantly slower than women without these alleles, while A*23:01, B*07:02, B*42:01, C*02:10, and C*07:02 were associated with increased HIV-1 susceptibility and rapid seroconversion [3, 5]. Combined genotypes including HLA-C1 + KIR2DL3 were reported as protective against HIV-1 infection among mother-to-child transmission but deleterious in sexual transmission [13]. Homozygosity for KIR3DS1 and KIR3DL1 high-expressing alleles in combination with HLA-B*57 was also reported to be associated with the HESN phenotype [5]. Our data do not replicate these and other previous reports. However, we do replicate another GWAS study that found no HLA or KIR genotypes associated with HIV-1 protection among HESN with hemophilia. It has been suggested that the parenteral transmission route and the high inoculum size override the innate resistance to HIV-1 conferred by the

Table 1. Distribution of Human Leukocyte Antigen Allele Frequencies in People With Human Immunodeficiency Virus (HIV) and HIV-Exposed Seronegative Subjects and Time to HIV-1 Seroconversion

Allele	All Alleles, No.	PWH Allele, No. (%)	HESN Allele, No. (%)	SP[a]	PWH vs HESN *P* Value	Adjusted *P* Value	OR (95% CI)	TTS Unadjusted *P* Value	Adjusted *P* Value
HLA-A (n = 1192)		574	618						
A*02	291	138 (24.0)	153 (24.8)	99	.95	1	1.05 (.7–1.3)	.87	1
A*01	157	70 (12.2)	87 (14.1)	99	.3	1	0.83 (.6–1.2)	.78	1
A*03	150	65 (11.3)	85 (13.8)	99	.17	1	0.75 (.5–1.1)	.3	1
A*24	116	59 (10.3)	57 (9.2)	99	.5	1	1.15 (.8–1.7)	.3	1
A*11	91	44 (7.7)	47 (7.6)	97	.9	1	1.01 (.6–1.6)	.5	1
A*29	77	42 (7.3)	35 (5.7)	95	.2	1	1.35 (.8–2.2)	.29	1
A*68	51	23 (4.0)	27 (4.4)	84	.7	1	0.91 (.5–1.6)	.98	1
A*30	49	26 (4.5)	23 (3.7)	83	.47	1	1.24 (.7–2.2)	.7	1
A*26	45	27 (4.7)	18 (2.9)	80	.09	1	1.68 (.9–3.1)	.19	1
A*32	41	20 (3.5)	21 (3.4)	75	.9	1	1.03 (.5–1.9)	.36	1
A*31	39	17 (3.0)	22 (3.6)	73	.6	1	0.82 (.4–1.6)	.86	1
A*23	31	18 (3.1)	13 (2.1)	64	.2	1	1.53 (.7–3.2)	.62	1
A*33	28	10 (1.7)	18 (2.9)	59	.17	1	0.59 (.3–1.3)	.34	1
A*25	26	14 (2.4)	12 (1.9)	55	.5	1	1.27 (.6–2.8)	.67	1
HLA-B (n = 1272)		618	654						
B*44	170	92 (14.9)	78 (11.9)	99	.11	1	1.33 (.9–1.9)	.07	1
B*35	139	65 (10.5)	74 (11.3)	99	.56	1	0.9 (.6–1.3)	.2	1
B*07	137	56 (9.1)	81 (12.4)	99	.033	1	0.66 (.5–.97)	.28	1
B*08	97	41 (6.6)	56 (8.6)	97	.15	1	0.73 (.5–1.1)	.7	1
B*51	91	56 (9.1)	35 (5.4)	97	**.0093**	**0.56**	1.82 (1.2–2.9)	.1	1
B*15	83	43 (7.0)	40 (6.1)	96	.57	1	1.14 (.7–1.8)	.57	1
B*40	75	36 (5.8)	39 (6.0)	94	.8	1	0.96 (.6–1.6)	.5	1
B*18	75	40 (6.5)	35 (5.4)	90	.4	1	1.22 (.8–1.9)	.9	1
B*14	63	27 (4.4)	36 (5.5)	82	.3	1	0.76 (.5–1.3)	.3	1
B*27	46	20 (3.2)	26 (4.0)	80	.4	1	0.79 (.4–1.4)	.57	1
B*57	45	18 (2.9)	27 (4.1)	70	.2	1	0.68 (.4–1.3)	.29	1
B*13	35	12 (1.9)	23 (3.5)	70	.07	1	0.53 (.3–1.1)	.048	1
B*38	35	20 (3.2)	15 (2.3)	60	.3	1	1.42 (.7–2.8)	.4	1
B*49	29	18 (2.9)	11 (1.7)	60	.15	1	1.75 (.8–3.8)	.56	1
B*55	29	13 (2.1)	16 (2.4)	50	.6	1	0.82 (.4–1.7)	.4	1
B*50	23	13 (2.1)	10 (1.5)	46	.45	1	1.37 (.6–3.2)	.56	1
B*37	20	12 (1.9)	8 (1.2)	46	.3	1	1.59 (.6–3.9)	.6	1
B*39	20	8 (1.3)	12 (1.8)	43	.4	1	0.69 (.3–1.7)	.6	1
B*52	19	11 (1.8)	14 (2.1)	31	.6	1	0.81 (.4–1.8)	.5	1
B*58	13	5 (0.8)	8 (1.2)	25	.4	1	0.65 (.2–2)	.26	1
B*45	11	8 (1.3)	3 (0.5)	23	.11	1	2.83 (.7–10.8)	.87	1
B*41	10	4 (0.6)	6 (0.9)	20	.57	1	0.69 (.2–2.5)	.7	1
HLA-C (n = 1186)		578	608						
C*07	265	117 (20.2)	148 (24.3)	99	.045	1	0.72 (.5–.99)	.17	1
C*04	151	75 (13.0)	76 (12.5)	99	.79	1	1.05 (.7–1.5)	.47	1
C*03	144	70 (12.1)	74 (12.2)	99	.97	1	0.99 (.7–1.4)	.2	1
C*06	120	56 (9.7)	64 (10.5)	99	.61	1	0.9 (.6–1.3)	.5	1
C*05	114	62 (10.7)	52 (8.6)	98	.18	1	0.63 (.4–.9)	.12	1
C*12	85	41 (7.1)	44 (7.2)	96	.9	1	0.98 (.6–1.5)	.67	1
C*16	76	38 (6.6)	38 (6.3)	94	.8	1	1.06 (.7–1.7)	.8	1
C*08	67	30 (5.2)	37 (6.1)	92	.49	1	0.84 (.5–1.4)	.5	1
C*01	47	25 (4.3)	22 (3.6)	82	.5	1	1.21 (.7–2.2)	.38	1
C*02	47	22 (3.8)	25 (4.1)	82	.78	1	0.92 (.5–1.7)	.38	1
C*15	47	27 (4.7)	20 (3.3)	82	.2	1	1.46 (.8–2.7)	.9	1
C*14	22	15 (2.6)	7 (1.2)	49	.06	1	2.32 (.9–5.8)	.17	1

Only alleles with >10 cases are shown. Uncorrected significant *P*-values are in bold.

Abbreviations: CI, confidence interval; HESN, human immunodeficiency virus–exposed seronegative; HLA, human leukocyte antigen; OR, odds ratio; PWH, people with human immunodeficiency virus; SP, statistical power; TTS, time to seroconversion.

[a]Statistical power (%) to detect association according to the allele frequency, the number of cases, a *z* value corresponding to α level for 5%, and OR of 2.5.

Table 2. Distribution of Killer Cell Immunoglobulin-like Receptor Alleles and Copy Frequencies Among People With Human Immunodeficiency Virus (HIV) and HIV-Exposed Seronegative Subjects and Time to HIV-1 Seroconversion

KIR	PWH Copies (0/1/2)	HESN Copies (0/1/2)	Gene copies in PWH vs HESN Adjusted *P* Value	PWH Allele, No. (%)	HESN Allele, No. (%)	PWH vs HESN Adjusted *P* Value	OR (95% CI)	TTS Unadjusted *P* Value
3DS1	323/24/0	331/30/2	1	24 (3)	32 (4)	1	0.7 (.4–1.3)	.56
3DL1	0/25/322	2/30/331	1	347 (49)	361 (51)	1	…	…
2DS5	343/4/–	357/6/–	1	4 (0.6)	6 (0.8)	1	0.6 (.2–2.1)	…
2DS4WT	347/0/–	362/1/–	1	0 (0)	1 (0.1)	…	…	…
2DS4TOTAL	–/4/343	–/11/352	1	347 (49)	363 (51)	…	…	…
2DS4DEL	4/57/286	4/54/305	1	343 (48)	359 (51)	1	0.9 (.2–3.8)	…
2DS2	300/46/1	313/49/1	1	47 (7)	50 (7)	1	0.9 (.6–1.5)	.26
2DS1	322/25/0	331/30/2	1	25 (3)	32 (4)	1	0.8 (.5–1.4)	.56
2DL1	–/–/347	–/–/363	…	347 (49)	363 (51)	…	…	…
2DL2	300/46/1	315/47/1	1	47 (7)	50 (7)	1	0.9 (.6–1.5)	.32
2DL3	1/46/300	1/48/314	1	346 (49)	362 (51)	1	0.9 (.06–15.3)	…
2DL4	–/–/347	–/–/363	…	347 (49)	363 (51)	…	…	…
2DL5A	346/1/–	363/0/–	1	1	1	1	1.05 (.07–16.8)	…
2DL5B	325/33/0	339/22/2	1	22 (3.1)	24 (3.4)	1	0.9 (.5–1.7)	.97
2DP1	–/2/345	–/2/361	1	347 (49)	363 (51)	…	…	…

Abbreviations: CI, confidence interval; HESN, human immunodeficiency virus–exposed seronegative; KIR, killer cell immunoglobulin-like receptor; OR, odds ratio; PWH, people with human immunodeficiency virus; TTS, time to seroconversion.

HLA-KIR system [4]. HIV-1 acquisition through sexual transmission does not appear to be influenced by either HLA-I or KIR genes among our population of White individuals.

One limitation of our study is the level of complexity of the HLA-KIR system in relation to HIV-1 infection. Epistatic interaction between specific HLA alleles and their KIR partners has been described and reduces the power to detect genetic associations. In a remarkable article, Martin et al discovered that while HLA-B Bw4 or KIR3DS1 independently does not have a significative impact on HIV-1 disease progression to AIDS, the co-occurrence of HLA-B Bw4 with isoleucine at position 80 (instead of threonine) plus KIR3DS1 was associated with a significant delay in disease progression [13]. Moreover, genetic variation at KIR3DS1 influences expression levels and target-cell killing upon binding to their ligands [13]. Additionally, the combined genotype HLA-B Bw4(80I) + KIR3DL1*h/*y was associated with a significant delay in progression and lower viral load [14]. The negative results presented here may be influenced by sample size or underrepresentation of potentially protective genotypes. Given the sample size and HLA allele frequency, this GWAS had an 80% power to detect OR >2.5 at the nominal *P* value; however, the power diminished significantly in alleles with lower frequency.

Contrary to the literature showing that the HLA-B*51 allele correlated with slow disease progression and reduction of viral load due to strong $CD8^+$ lymphocyte responses to Gag and Pol proteins [15], our data suggest that this allele is correlated with a modest increased risk of HIV-1 infection in sexually exposed individuals (OR, 1.82 [95% CI, 1.2–2.9]). Of note, the HLA-B*51 allele has been strongly linked to Behçet disease, a multisystem inflammatory disorder.

In summary, the data do not support a major role of the HLA and KIR alleles in susceptibility to HIV-1 infection through the sexual route of transmission. However, the cohort included in this study is too small to completely rule out a role for HLA/KIR, particularly given the low frequency of many of the alleles under study. Our results indicate that the genetic basis of HIV-1 viral load and disease progression are different from the genetics of HIV-1 infection susceptibility, a paradox that merits further investigation.

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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Potential conflicts of interest. The authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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