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Relationship between human leukocyte antigen alleles and risk of Kaposi's sarcoma in Cameroon

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Abstract

Several studies published to date report associations between human leukocyte antigen (HLA) alleles and different types of Kaposi's Sarcoma (KS). However, there is little concordance between the HLA alleles identified and the populations studied. To test whether HLA alleles associate with KS in a Cameroonian case-control study, we performed high-resolution HLA typing in KSHV seropositive individuals. Among HIV-positive individuals, carriers of *HLA-B*14:01* were at a significantly higher risk of AIDS-KS ($p = 0.033$). For HIV-negative patients, a gene-wise comparison of allele frequencies identified the *HLA-B* ($p = 0.008$) and *-DQA1* ($p = 0.002$) loci as possible risk factors for endemic KS. Our study provides additional understanding of genetic determinants of KS and their implications in disease pathogenesis. Further validation of these findings is needed to define the functional relevance of these associations.

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Introduction

Kaposi's sarcoma is an angioproliferative disease with a multifocal presentation ranging from indolent vascular nodules in the skin to a more aggressive course with widespread involvement of lymph nodes, mucosae, and internal organs [1, 2]. Kaposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus-8) is the causative agent of all forms of KS. Of the four epidemiological sub-types of KS, endemic KS, and AIDS-KS are among the most common cancers in sub-Saharan Africa [3, 4]. Endemic KS is observed in both HIV-negative children and adults and can run a more aggressive course in children before puberty [5, 6]. In HIV-positive individuals with KS, the mortality rate is twice as high as in HIV-positive individuals without KS [7, 8].

The pathogenesis of KS is complex and KS risk is associated with several behavioral and environmental factors [9–12]. Few studies, however, have examined host genetic risk factors for KS [13–15]. The first studies on associations between human leukocyte antigen (HLA) alleles and KS were performed prior to the discovery of KSHV as the causative agent [16–21]. Most recently, HLA association studies of KS have mainly focused on AIDS-KS [22–26], with few investigating transplant-related KS [27–30] or classic KS [31–34]. Some of these studies have identified both HLA class I [22, 23, 27, 33, 35] and class II [24, 33] as associated with an increased risk for KS. However, based on the heterogeneity of populations studied, the diversity in HLA genotyping techniques and genotype resolution, the reported associations have been inconsistent across studies.

Sub-Saharan African populations are still among the most under-represented populations in human genetic studies and reports on HLA associations with KSHV or endemic KS are rare. We recently reported on epidemiological risk factors for AIDS-KS and endemic KS on a large case–control study in Cameroon, in which ethnicity was most impactful [11]. The present study seeks to determine whether specific associations between HLA alleles and the risk of endemic or AIDS-KS are present in KSHV seropositive individuals of that Cameroon case–control study.

Results and discussion

To identify possible immunogenetic risk factors for both AIDS-KS and endemic KS, high-resolution HLA genotyping was performed using genomic DNA from 943 KSHV seropositive individuals from Cameroon. Of these, 680 individuals (157 cases, 523 controls) were HIV-positive and 263 (14 cases, 249 controls) were HIV-negative (Fig. 1). The average age was 39 (interquartile range [IQR], 33–47) and 38 (IQR, 32–47) in HIV-positive and HIV-negative individuals, respectively. No differences in age and gender were observed between AIDS-KS cases and HIV-positive controls (Fig. 1). In the HIV-negative group, however, cases were exclusively male and significantly older than controls.

HLA locus-specific associations with KS were analyzed by comparison of the allele distribution in HIV-positive or HIV-negative cases and controls (Table 1). Of the seven HLA loci, only *HLA-B* and *-DRB1* were significant for AIDS-KS after correction for multiple testing (false discovery rate (FDR) < 0.05). For endemic KS, only *HLA-B* and *-DQA1*

remained statistically significant. As such, the HLA locus-specific data indicated that both HLA class I and class II loci may contribute to the risk of KS in HIV-positive and HIV-negative individuals.

At high-resolution level (Table 2), the HLA allele-specific analysis showed *HLA-B*14:01* (odds ratio (OR) = 4.27 [95% confidence interval (CI), 1.67–10.91]) to be associated with an increased risk of AIDS-KS in HIV-positive individuals (FDR = 0.03). In HIV-negative individuals, four alleles were associated with endemic KS. However, analyses using multivariate models indicated that these associations may be confounded by age and gender.

The association of *HLA-B*14:01* with AIDS-KS is consistent with previous reports, in which *HLA-B*14* alleles were observed at higher frequency in AIDS-KS patients in the USA (including B14 [25], *HLA-B*14:01* [22] and *HLA-B*14:02* [23]). These data suggest that carriage of *HLA-B*14* (16.5% and 6.5% of HIV-positive cases and controls, respectively) may be either a true risk factor for KS or be confounded through linkage disequilibrium (LD) with a causal, though to us unknown, locus. The observed allele frequency for *HLA-B*14:01* in our controls is similar to the frequencies reported for sub-Saharan populations in the allele frequency net database [36] (data not shown). Nevertheless, due to the small number of cases, further studies are required to validate the results and to account for potential population stratification and the possible role of gender within our case-control study. Preceding reports identified numerous HLA class II alleles as possible risk factors for AIDS-KS in Caucasians [23, 24]. The previously reported risk alleles vary and within our cohort of Cameroonian AIDS-KS patients, none of the identified class II associations withstood correction for multiple testing. Certain associations may be ethnicity- and geography-dependent, and as such cannot be replicated in our cohort. Further, the comparison of associations between studies may be impacted by differences in HLA typing methods and bias introduced by the overall small number of participants per study (mean of 430 participants in five AIDS-KS studies). With the standardization of typing methods and reporting of associations, a more comprehensive analysis of HLA associations across different populations may help evaluate the effect of individual HLA alleles to the risk of KS.

To our knowledge, this is the first study to investigate the role of HLA associations and the risk of endemic KS in a sub-Saharan population. The HIV-negative cohort investigated in this study is significantly different from the HIV-positive group, as all cases are exclusively older, male patients. Observations by the study coordinators indicate that older men were less likely to attend the hospital for HIV-testing and as such, recruiting the appropriate older, male controls was challenging. Although *HLA-B* and *-DQA1* were identified as significant loci for endemic KS, the allele-specific associations should be regarded with caution. The overall results were replicated if female HIV-negative controls were excluded from the analysis to account for the age and gender bias observed in our cohort (data not published). Yet, a more comprehensive investigation of these associations may help evaluate the effects of specific HLA alleles on endemic KS and mitigate the bias observed in our cohort.

This study identified an association between *HLA-B*14:01* and AIDS-KS and as such, replicates previous reports on associations between HLA-B14 and risk of KS in Caucasian,

HIV-positive individuals [22, 23, 25]. Additional studies are needed to evaluate if the associations described have any functional effect on the immunemediated response to KSHV [37] or the pathogenesis of KS. Observations by others indicate that non-classical HLA associations [22] and other genetic factors may also play a role in the susceptibility of AIDS-KS. In order to assess non-HLA determinants, further studies are underway investigating the role of polymorphisms of immunomodulatory genes in KS.

Methods

Study participants

As described previously [11], HIV-positive and HIV-negative KS cases were recruited between 2009 and 2011 from within the IeDEA-Central Africa cohort, by referral to the Oncology Department of the General Hospital and through the SOcieté CHIMIOthérapie (SOCHIMIO) cancer registry in Yaoundé. HIV-positive and HIV-negative controls were identified at the HIV Care and Treatment or the Voluntary Testing and Counseling Centers of the General Hospital and the Military Hospital. Study participants gave informed consent according to the declaration of Helsinki, were 21 years or older and had resided in Cameroon for a minimum of 6 months prior to enrollment. Each KS case was matched to HIV-positive and -negative controls (4:1 and 2:1, respectively) by sex and 5-year age bands. KS was diagnosed through clinical examination by trained cancer specialists and if warranted through skin biopsy. This study was approved by the Cameroon National Ethics Committee and the Institutional Review Board at RTI International.

Specimens, KSHV serodiagnosis, and DNA preparation

Whole blood, serum, and saliva samples were collected from all participants at enrollment of the study. KSHV antibodies levels against the recombinant K8.1 and ORF73 antigens were measured by ELISA as previously published [38]. Participants were classified as seropositive if they had above-cutoff antibody levels against either antigen. Whole blood was collected in PAXgene tubes and DNA was extracted using the PAXgene Blood DNA kit as per the manufacturer's protocol (PreAnalytix, Hombrechtikon, Switzerland). Saliva DNA was extracted using the Qiagen DNA Blood mini kit following the manufacturer's instructions (Qiagen, Hilden, Germany). DNA was quantified by fluorometry using the Qubit dsDNA BR Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA).

High-resolution sequence-based HLA typing

HLA typing was performed on either blood or saliva derived DNA using a targeted next generation sequencing method. Briefly, locus-specific primers are used to amplify a total of 24 polymorphic exons of *HLA-A*, *-B*, *-C* (exons 1 to 4), *-DPA1* (exon 2), *-DPB1* (exons 2 and 3), *-DQA1* (exons 1 and 2), *-DQB1* (exons 2 and 3), *-DRB1* (exons 2 and 3), and *DRB3,4,5* (exon 2) genes with Fluidigm Access Array (Fluidigm Singapore PTW Ltd, Singapore). The Fluidigm PCR amplicons were pooled and subjected to sequencing either on the Roche 454 platform (Roche, Indianapolis, IN, USA) or the Illumina MiSeq platform (Illumina, San Diego, CA, USA). HLA alleles and genotypes were called using the Omixon HLA Explore (beta version) software (Omixon, Budapest, Hungary). The *HLA-DRB3*, -

DRB4, and *-DRB5* genes were not included in the analysis as genotypes could only be determined for part of the cohort.

Statistical analysis

Associations were tested in 946 KSHV seropositive individuals, investigating AIDS-KS (HIV-positive, $n = 680$) and endemic KS (HIV-negative, $n = 263$)-specific associations. Non-genetic factors such as age ($\log_{10}$ transformed) and gender were assessed individually for the association with case/control status using Welch's Two Sample t -test or Pearson's Chi-squared (χ^2) test, respectively. To assess HLA locus-specific associations, we assessed the differences of HLA loci in cases and controls from 2xN contingency tables using a χ^2 test [clump.c [39]]. The false discovery rate (FDR), calculated in R [40], was used to adjust for multiple testing. The association between individual HLA alleles and KS was tested using gPLINK v2.05 in combination with PLINK v1.90 [41] in loci identified to be linked to KS. Within PLINK, P value, odds ratio (OR) and the 95% confidence interval (CI) were calculated for each allele in the HIV-positive group. In HIV-negative individuals, a multivariate regression model was performed to control for possible effects of age and gender. Correction for multiple comparisons was performed using FDR.

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Fig. 1. Schematic representation of KSHV-positive, HIV-positive, and HIV-negative cohorts. **a** Welch Two Sample *t*-test; **b** Pearson's Chi-squared test. *IQR* interquartile range

Table 1

Association analysis for seven HLA loci in either HIV-positive (AIDS-KS) or HIV-negative (Endemic-KS) KS cases and controls

Locus	AIDS-KS <i>N</i> = 680		Endemic-KS <i>N</i> = 263	
	χ^2	<i>P</i> -value	χ^2	<i>P</i> -value
HLA-A	28.85	0.118	38.28	0.033
HLA-B	44.55	0.001 ^a	41.26	0.008 ^a
HLA-C	27.15	0.051	13.63	0.673
HLA-DPB1	10.82	0.282	20.10	0.025
HLA-DQA1	18.39	0.079	38.08	0.002 ^a
HLA-DQB1	12.87	0.233	18.52	0.053
HLA-DRB1	23.73	0.012 ^a	19.41	0.060

A total of 943 KSHV seropositive individuals from Cameroon were included in the analysis. *P*-values were derived from 2xN contingency tables using a Chi-squared (χ^2) test. Statistically significant associations are indicated in bold

^aDenotes associations that withstand correction for multiple testing using the false discovery rate (FDR < 0.05)

Table 2

Associations of individual *HLA-A*, *-B*, *-DPB1*, *-DQA1*, and *-DRB1* alleles in KSHV-positive, HIV-positive, or -negative individuals with KS

HLA allele	AIDS-KS (N = 680)				Endemic KS (N = 263)			
	Allele frequency		FDR	OR [95% CI]	Allele frequency		FDR	OR [95% CI]
	Cases	Control			Cases	Control		
<i>B*07:02</i>	0.07	0.09	0.477	0.73 [0.45–1.20]	0.11	0.05	0.650	2.09 [0.59–7.37]
<i>B*08:01</i>	0.02	0.02	0.659	1.23 [0.51–2.96]	0.00	0.02	0.700	NA
<i>B*14:01</i>	0.03	0.01	0.033	4.27 [1.67–10.91]	0.04	0.00	0.196	9.19 [0.81–104.5]
<i>B*14:02</i>	0.03	0.01	0.291	2.25 [0.91–5.56]	0.11	0.02	0.095	4.86 [1.29–18.33]
<i>B*14:03</i>	0.03	0.01	0.358	1.93 [0.80–4.64]	0.00	0.02	0.700	NA
<i>B*15:03</i>	0.03	0.04	0.358	0.57 [0.27–1.22]	0.04	0.05	0.833	0.7 [0.09–5.37]
<i>B*15:10</i>	0.02	0.04	0.358	0.52 [0.22–1.23]	0.00	0.03	0.692	NA
<i>B*15:16</i>	0.01	0.02	0.519	0.52 [0.15–1.77]	0.04	0.03	0.954	1.12 [0.14–8.73]
<i>B*18:01</i>	0.05	0.03	0.267	1.89 [0.99–3.61]	0.04	0.03	0.939	1.19 [0.15–9.37]
<i>B*35:01</i>	0.05	0.08	0.291	0.60 [0.35–1.04]	0.00	0.08	0.515	NA
<i>B*42:01</i>	0.05	0.03	0.519	1.41 [0.76–2.61]	0.00	0.06	0.558	NA
<i>B*44:03</i>	0.05	0.07	0.523	0.77 [0.44–1.35]	0.29	0.06	<0.001	6.24 [2.54–15.34]
<i>B*44:07</i>	0.03	0.01	0.329	2.03 [0.88–4.68]	0.00	0.02	0.700	NA
<i>B*45:01</i>	0.03	0.04	0.523	0.72 [0.36–1.43]	0.04	0.06	0.743	0.58 [0.08–4.4]
<i>B*49:01</i>	0.06	0.07	0.566	0.82 [0.49–1.38]	0.00	0.06	0.558	NA
<i>B*51:01</i>	0.01	0.02	0.523	0.55 [0.16–1.88]	0.00	0.01	0.743	NA
<i>B*53:01</i>	0.14	0.09	0.118	1.67 [1.13–2.45]	0.07	0.08	0.908	0.84 [0.19–3.64]
<i>B*57:03</i>	0.02	0.03	0.566	0.71 [0.29–1.73]	0.04	0.03	0.954	1.12 [0.14–8.73]
<i>B*58:01</i>	0.05	0.05	0.687	0.89 [0.49–1.59]	0.04	0.07	0.700	0.49 [0.06–3.71]
<i>B*58:02</i>	0.11	0.12	0.641	0.90 [0.60–1.34]	0.11	0.08	0.804	1.3 [0.38–4.5]
<i>B*81:01</i>	0.04	0.03	0.566	1.30 [0.66–2.57]	0.00	0.03	0.692	NA
<i>DQA1*01</i>	-	-	-	-	0.14	0.03	0.037	5.02 [1.56–16.17]
<i>DQA1*01:01</i>	-	-	-	-	0.00	0.04	0.686	NA
<i>DQA1*01:02</i>	-	-	-	-	0.64	0.37	0.041	3.07 [1.39–6.8]
<i>DQA1*01:03</i>	-	-	-	-	0.00	0.02	0.700	NA
<i>DQA1*01:05</i>	-	-	-	-	0.00	0.03	0.700	NA

HLA allele	AIDS-KS (N = 680)				Endemic KS (N = 263)			
	Allele frequency		FDR		Allele frequency		FDR	
	Cases	Control	Cases	Control	Cases	Control	Cases	Control
<i>DQA1*02:01</i>	-	-	-	-	0.00	0.07	0.526	NA
<i>DQA1*03</i>	-	-	-	-	0.18	0.04	0.005	5.8 [1.98–16.99]
<i>DQA1*03:03</i>	-	-	-	-	0.00	0.10	0.407	NA
<i>DQA1*04</i>	-	-	-	-	0.00	0.04	0.673	NA
<i>DQA1*04:01</i>	-	-	-	-	0.00	0.09	0.428	NA
<i>DQA1*05:01</i>	-	-	-	-	0.00	0.05	0.650	NA
<i>DQA1*05:05</i>	-	-	-	-	0.00	0.06	0.558	NA
<i>DRB1*01:02</i>	0.03	0.05	0.519	0.67 [0.34–1.34]	-	-	-	-
<i>DRB1*03:01</i>	0.04	0.07	0.180	0.48 [0.25–0.91]	-	-	-	-
<i>DRB1*03:02</i>	0.07	0.04	0.231	1.76 [1.03–2.99]	-	-	-	-
<i>DRB1*07:01</i>	0.04	0.05	0.566	0.81 [0.44–1.47]	-	-	-	-
<i>DRB1*08:04</i>	0.06	0.07	0.566	0.82 [0.48–1.40]	-	-	-	-
<i>DRB1*11:01</i>	0.11	0.07	0.118	1.75 [1.13–2.69]	-	-	-	-
<i>DRB1*11:02</i>	0.03	0.03	0.639	0.80 [0.37–1.76]	-	-	-	-
<i>DRB1*12:01</i>	0.06	0.05	0.566	1.21 [0.70–2.11]	-	-	-	-
<i>DRB1*13:01</i>	0.17	0.14	0.523	1.18 [0.83–1.66]	-	-	-	-
<i>DRB1*13:02</i>	0.07	0.05	0.519	1.32 [0.78–2.22]	-	-	-	-
<i>DRB1*13:03</i>	0.01	0.02	0.329	0.38 [0.11–1.26]	-	-	-	-
<i>DRB1*15:03</i>	0.27	0.31	0.427	0.82 [0.62–1.09]	-	-	-	-

Only associations with loci identified as significant in Table 1 are included. Associations in HIV-positive individuals were determined by a χ^2 test. Statistically significant associations, which withstand correction for multiple testing are shown in bold

CI confidence interval, FDR false discovery rate, NA odds ratio was not calculated due to low allele frequency, OR odds ratio