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HLA Class I Haplotypes of HIV-1-Infected Persons on Likoma Island, Malawi

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Abstract

Human leukocyte antigen (HLA) allele frequencies vary between different human populations, with implications both for the evolutionary pressures shaping those populations as well as the outcome of new infectious epidemics. We defined HLA class I types in a well-described cohort of persons on Likoma Island in Malawi, a population for which there are lacking data on allelic frequencies. The profile of HLA frequencies was similar but phylogenetically distinct from those of other sub-Saharan African populations in neighboring regions. The most common A alleles included A30, A23, A28 (A*68), and A2, and the most common B alleles included B15 (group), B53, B58, and B44. Notably, the frequency of B53, which is protective against malaria, was similar to that of other malaria-endemic African countries, and higher than that in countries with less malaria. This is the first reported significant dataset of HLA class I allelic frequencies in Malawians.

Keywords

HLA; Malawi

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1. INTRODUCTION

Human leukocyte antigen (HLA) genes are the most polymorphic genes within the human genome. Examination of HLA types in human populations has revealed that different ethnic and geographic groups have varying distributions of polymorphisms, which can be utilized to infer anthropologic relationships. This approach has been a useful tool in the study of human evolutionary history.

HLA genetic polymorphisms also have key implications in medicine. HLA complexes present peptide sequences for recognition by T lymphocytes, and therefore are crucial for cellular immunity. Differing HLA types vary in the motifs of peptide sequences that they bind (epitopes), and therefore the HLA profile of a person is a key determinant of the epitope targeting of foreign proteins from infecting pathogens, or the targeting of self-proteins in autoimmune disease. Individual HLA polymorphisms have been shown to correlate to risk of autoimmunity, as well as outcomes in infectious diseases.

As the origin of humans, Africa harbors great human genetic diversity, which is mirrored by the high degree ethnic diversity seen on the continent. HLA studies of Africans have defined HLA profiles of some ethnic groups, but many populations remain uncharacterized. Although there has been a report of HLA class II typing in 328 persons from Malawi [1], there has been only one small survey including 45 Malawian HLA class I profiles that has been reported but not published [2]. Malawi is a land-locked southern African nation that has ethnically distinct populations, several of which are subgroups of the Bantu. The country is mostly rural and supported by subsistence agriculture and local small-scale trade, and therefore has limited immigration and population mixing.

The Likoma Network Study in Malawi examines sexual networks of all adults in seven villages on Likoma Island (Figure 1) in Lake Malawi [3, 4]. The population of the island is approximately 73% Nyanja and 15% Tonga ethnicities, and the remainder is a variety of individuals from diverse ethnic groups in Malawi or Tanzania (Chewa, Tumbuka, Swahili, Yao, and others). The economic development of the island is generally low, and small-scale fishing is the main support of most households. Transportation to and from Likoma is fairly limited, with only one regularly scheduled boat transport to mainland Malawi per week, although a few small canoes travel daily to Mozambique and neighboring Chizumulu Island. Here we examine HLA class I types for participants of the Likoma Network Study, which provides subjects of defined ethnicity for examination of Malawian HLA polymorphisms. These data provide insight into the characteristics of these populations, with implications for vaccines and immunopathogenesis of infectious diseases such as HIV and malaria in southern Africa.

2. MATERIALS AND METHODS

2.1. Subjects

The Likoma Network Study is a study of risk factors for HIV-1 transmission, conducted initially among seven villages of the island, and subsequently extended to all island localities. As part of the study, respondents were offered the possibility of participating in HIV-1 testing and counseling. At that stage, dried blood spots were collected from 167 participants of the Likoma Network Study; 157 were HIV-1-infected by serology, and 10 were HIV-1-uninfected controls. Dried blood spots were collected by trained testing and counseling providers, usually in the participant's home following testing and counseling. Written consent from each participant was obtained prior to sample collection, under an IRB-approved protocol. Participants were free to refuse donation of dried blood spots after choosing to participate in HIV-1 testing and counseling.

2.2. Sample collection and genomic DNA extraction

Blood droplets were collected onto S&S 903 filter paper by finger lancet, and allowed to dry at room temperature. A 5 to 10 mm diameter portion of each dried blood spot was incubated overnight at 68°C in extraction buffer (10mM Tris ph 8.0, 50mM KCl, 0.45% Tween 20, 0.45% NP-40) plus proteinase K (1.33 mg/ml final concentration). The DNA in the supernatant was then purified using the Qiagen (Hilden, Germany) DNeasy DNA purification Kit according to the manufacturer's protocol. DNA was eluted in 200μL of AE buffer pre-heated to 68°C. The quantity and purity of the DNA was confirmed by spectrophotometry. Samples typically yielded 50μg/mL of DNA with an A260/280 ratio of greater than 1.6. A total of 1μg of genomic DNA was used for subsequent HLA typing.

2.3. HLA typing

DNA-based HLA-A, B, and C typing was performed using LABType® SSO DNA typing reagents (One Lambda, Canoga Park, CA) according to the manufacturer's specifications, and probe hybridization was analyzed on the Luminex 100 instrument (Luminex, Austin, TX). Genotype determination and data analysis were performed using the HLA Visual software program (One Lambda, Canoga Park, CA) according to the manufacturer's instructions.

2.4. Statistical analysis for Hardy-Weinberg equilibrium

All alleles at each locus plus an unidentified allele (blank) were considered for analyses. Maximum likelihood estimates of HLA allele frequencies were calculated according to the "gene-counting" iterative procedure of Smith [5], which is an example of the EM algorithm applied to multinomial data [6]. Pearson's chi-square statistic was used for testing Hardy-Weinberg equilibrium with k(k-1)/2 degrees of freedom (d.f.), where k equals the number of identified alleles at each locus. A P-value <5% was considered statistically significant to infer a lack-of-fit.

2.5. Phylogenetic assessment

HLA data from our cohort were compared to previously published HLA frequencies in different ethnic populations, including Botswanans [7], Congolese [8], Namibian San Bushmen [9], South African Xhosas and Whites [10], South African Blacks who were primarily Zulu [11, 12], Nigerians [13], Zimbabwean Blacks [14], Gambians [15], Malians [16], Ugandans [17], Equatorial Guineans [18], Rwandans [19], Zambians [20], United States American Blacks [15, 21, 22], South African Whites [10], British Whites [13], Europeans [23], and Japanese [23]. Only HLA types (low resolution) for which unambiguous and complete comparisons (molecular versus serological typing) could be made across all datasets were utilized (A-alleles 01, 02, 03, 11, 23, 24, 25, 26, 29, 30, 31, 32, 33, 34, and 36; B-alleles 07, 08, 13, 14, 18, 27, 35, 37, 39, 40, 41, 42, 44, 45, 47, 48, 49, 50, 51, 52, 53; C-alleles 01, 02, 03, 04, 05, 06, 07, 08). A phylogenetic tree was constructed based on Nei's D_A distances using the neighbor-joining method with 1000 bootstrap replications, computed using the freeware program POPTREE2 [24] running on a Macintosh Pro.

3. RESULTS

Genomic DNA extractions were performed on dried blood spots from 167 persons from the Likoma Network Study. Of these, there was sufficient DNA recovery for HLA class I typing at A, B, and C loci for 152 samples (including 142 from persons with HIV-1 infection and 10 from uninfected persons). Among all participants, there were 16 HLA A allele groups, 18 HLA B allele groups, and 13 HLA C allele groups detected; allele group frequencies are

indicated in Table 1. The majority of these persons self-reported as Nyanja ethnicity (106/157, 68%), followed by Tonga (14/157, 9%), Chewa (12/157, 8%), Ngoni (8/157, 5%), and Tumbuka (3/15, 2%), and the remainder had unknown/unreported ethnicity (13/157, 8%).

The most frequent HLA A alleles were A30, A23, A28 (A*68), and A2, which together accounted for nearly 60%, and the most common B alleles were the B15 (B*15) group (B62, B63, B70, B71, B72), B53, B58, and B44, which together accounted for over 50% (Table 1). Nyanja versus other ethnicities had similar HLA frequencies (not shown), and thus all subjects were considered as a single group. Given the survey nature of the study in a geographic area with extended families, non-random sampling of subjects (i.e. related individuals) was a concern when computing representative frequency estimates. However, the data appeared to satisfy the conditions of the Hardy-Weinberg equilibrium at each locus, mitigating this concern. Chi-square test statistics equaled 132.32 (d.f. = 136, P = 0.57), 265.32 (d.f. = 253, P = 0.28) and 71.79 (d.f. = 105, P = 0.99) for the A, B and C loci, respectively.

The frequencies of HLA class I types in this Malawian population were compared phylogenetically to those of previously reported African cohorts, as well as reference groups outside Africa (Figure 2). The Malawian population was most closely related to a cluster of populations mostly from southern African countries including Botswana, Namibia, and South Africa, although a population from Guinea also clustered with this group. The next closest branches on the phylogenetic tree represented populations from countries in the more central-southern region of Africa, including Zimbabwe, Zambia, Rwanda, and Uganda. Populations from Congo, Nigeria, Gambia, and Mali, as well as North American Blacks were more distantly related, and all of these populations were distinct from outgroups of Whites from South Africa, Britain, and Europe, as well as Japanese.

4. DISCUSSION

Given the central role of HLA molecules in cellular immunity, the rich allelic diversity of HLA is a reflection of the evolutionary pressure on humans to respond to various infectious challenges. Phylogenetic analyses demonstrate that different ethnic populations have diverged in their frequencies of HLA types, which has obvious evolutionary and clinical implications. In the current study we examine Malawians, a relatively uncharacterized human population for class I HLA types.

The data demonstrate that Malawians on Likoma Island form a phylogenetically distinct group in terms of HLA allelic distributions, which is related to other groups from neighboring areas in Africa. Some of the most common alleles in the Malawians (A23, A30, B53, B58) are uncommon in Caucasian or Asian populations, but similar to other African populations, consistent with the known evolutionary origins of these different groups. Although this HLA survey was limited to Likoma Island, the ethnic groups on the island mirror those in the region, and these ethnic groups all originate from the Bantu group. While the numbers were small, HLA allele distributions appeared similar between the different ethnicities found on Likoma Island.

HLA Class I alleles play key roles in the pathogenesis of several infectious diseases, including those of particular significance in sub-Saharan Africa. Allelic frequency may not only reflect the environmental pressures shaping the evolution of this variable genetic locus in humans, but also may influence the susceptibility of a population to new epidemics. Certain HLA alleles in Malawians are interesting in the context of infectious diseases of relevance to sub-Saharan Africa. The B53 allele, which is particularly common in the

Likoma Island cohort at about 12%, has been suggested to have a strong protective benefit against severe malaria [25]. B53 has a low frequency of <1% in Caucasians from South Africa [10], Britain [13], and Europe [23], as well as Japanese [23]. Interestingly, in other sub-Saharan African populations, B53 varies considerably in frequency, with a reported frequency of <1% in Namibian San Bushmen [9] and Guineans [18], but a frequency of about 22% in Nigerians [13], perhaps reflecting the distribution of malaria predominately across central Africa.

M-group HIV-1 has caused a relatively new pandemic, likely starting with a Chimpanzee to human transmission event in central Africa about 70 to 100 years ago [26, 27]. Exhaustive searches for genetic determinants of immune outcome in HIV-1 infection have identified HLA class I genes to have the strongest associations [28, 29]. Cohort-based studies, predominately in Western populations, have demonstrated specific associations of certain alleles with the altered rates of disease progression [30-35]. The most protective alleles identified have been B27 and B57, which are infrequent in our Malawian cohort and other studies of Africans, but more commonly found in American and European Caucasians. B35 has been associated with more rapid disease progression, and appears to be lower in frequency in our cohort (about 2%) compared to Caucasian groups where it runs from about 7 to 10% [10, 13, 23], although different B35 subtypes vary in their influence on disease [36], and we do not have breakdowns for B35 subtypes. Given the relatively recent initiation of the HIV-1 pandemic, it is likely that the virus has not yet influenced HLA frequencies in humans, but the pre-existing rates of certain HLA alleles may affect the spread of the virus in different human populations.

Of note, all but 10 of the 152 persons from whom HLA data were obtained were HIV-1-infected, and this is a potential source of sampling bias comparing the observed HLA frequencies to those in the general population of Likoma Island or Malawi. The overall frequency of HIV-1 infection was approximately 8% on Likoma Island [3, 4]. While HLA types have been linked to disease progression in infected persons, they are not believed to influence risk for infection. It is possible that the HIV-1-infected population was enriched for protective HLA types such as B*27 and B*57 and reduced for types associated with faster disease progression such as B*35, and that the frequencies of such HLA types were biased by survival. Overall, however, the frequencies of these alleles were very similar to those published for neighboring countries such as Zambia.

In summary, this study defines frequencies of HLA class I alleles in Malawians on Likoma Island, and shows that this group has a distinct profile compared to other African populations. The frequencies of certain key alleles that influence infectious disease pathogenesis vary in Malawians compared to Caucasians and other sub-Saharan African groups.

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Abbreviations

HLA	human leukocyte antigen
HIV	Human Immunodeficiency Virus

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Figure 1. Geographic location of Likoma Island

The location of Likoma Island on Lake Malawi (shaded, at the eastern border of Malawi) is indicated.

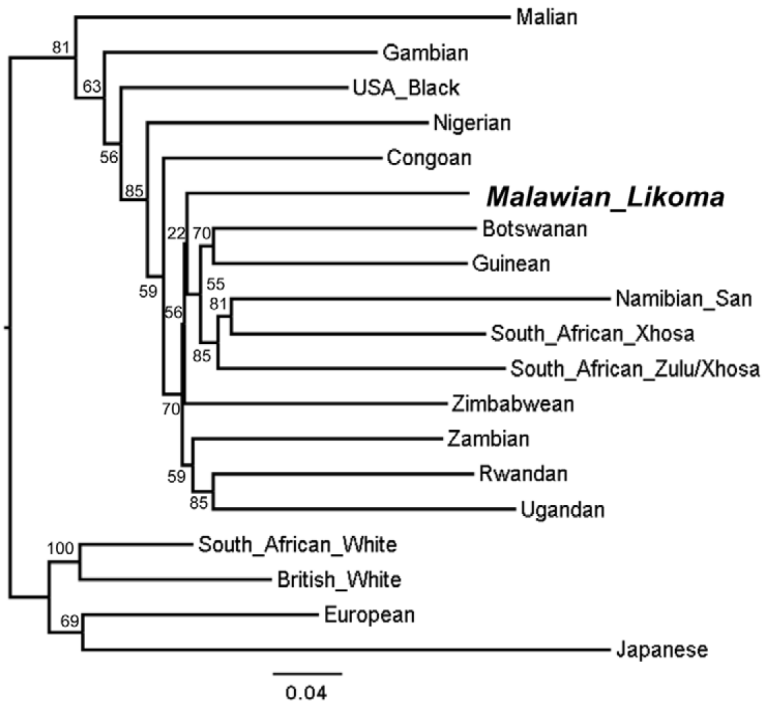

Figure 2. Phylogenetic relationships of Likoma Island inhabitants to other populations in Africa

D_A distances of allelic frequencies for selected HLA A-, B-, and C-alleles were calculated for the Likoma Island cohort in comparison to those reported for other ethnic groups. The results were utilized to create a neighbor-joining tree, with bootstrap values shown for 10,000 replicates.

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Table 1

Frequencies of HLA A alleles in the Likoma Island cohort

Allele Group	Gene Frequency	Allele Group	Gene Frequency	Allele Group	Gene Frequency
Blank	0.18%	Blank	0.00%	Blank	0.26%
A1	3.99%	B7	5.28%	C2	10.43%
A2	9.86%	B8	0.62%	C3	5.83%
A3	3.40%	B13	1.86%	C4	16.97%
A23	12.01%	B14	6.52%	C5	0.65%
A24	0.93%	B18	6.83%	C6	12.71%
A26	0.93%	B27	0.62%	C7	17.65%
A28	11.40%	B35	2.48%	C8	7.52%
A29	6.16%	B39	0.93%	C9	0.33%
A30	25.57%	B41	1.86%	C10	2.89%
A32	1.54%	B42	5.90%	C12	1.96%
A33	5.25%	B44	9.01%	C14	0.98%
A34	3.40%	B45	4.04%	C15	0.65%
A36	4.61%	B51	0.31%	C16	3.27%
A43	1.54%	B53	11.80%	C17	7.49%
A66	4.32%	B57	3.11%	C18	10.41%
A74	4.63%	B58	12.42%		
A80	0.31%	B62	0.62%		
		B63	0.93%		
		B67	0.31%		
		B70	10.25%		
		B71	5.90%		
		B72	0.31%		
		B81	8.07%		