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BRIEF COMMUNICATION

HLA alleles and haplotypes in Burmese (Myanmarese) and Karen in Thailand

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Abstract

This is the first report on human leukocyte antigen (HLA) allele and haplotype frequencies at three class I loci and two class II loci in unrelated healthy individuals from two ethnic groups, 170 Burmese and 200 Karen, originally from Burma (Myanmar), but sampled while residing in Thailand. Overall, the HLA allele and haplotype frequencies detected by polymerase chain reaction sequence-specific primer (PCR-SSP) at five loci (A, B, C, DRB1 and DRQB1) at low resolution showed distinct differences between the Burmese and Karen. In Burmese, five *HLA-B*15* haplotypes with different HLA-A and HLA-DR/DQ combinations were detected with three of these not previously reported in other Asian populations. The data are important in the fields of anthropology, transplantation and disease-association studies.

The human leukocyte antigen (HLA) classical class I and class II loci consist of members of a family of closely linked genes that are highly polymorphic with thousands of alleles that code for proteins with a major role in recognizing foreign antigens (1). The distributions of HLA alleles and haplotypes that are integral to the immune response and in the presentation of self and non-self peptides to T lymphocytes differ among populations in East Asia in a continuous pattern rather than highly distinct structures (2). Molecular analysis of the HLA diversity is critical to the investigation of disease associations and drug hypersensitivity and for selecting donors for tissue transplantation (3–6). These applications depend on obtaining reliable data concerning the frequencies of HLA genes and haplotypes of different ethnic groups within populations. In South East Asia, the population of Thailand in the central Indochina peninsula is approximately 68 million people consisting mainly (90%) of Thai/Dai and Thai–Chinese ethnicity, but with at least 70 minority ethnic groups including the small hill tribes such as the Karen and the Hmong, and the Burmese to the west of Thailand (7, 8). While there have been studies of HLA genetic structure of Southern Thai–Malay Muslims (9), northeast Thais (10) and different ethnic groups within Thailand (11, 12), HLA allele studies are lacking on the Burmese or Karen populations in neighboring Burma or those currently residing in Thailand as migrant workers or refugees. In this study, the allele and haplotype frequencies of HLA-A, -B, -C, -DRB1 and -DQB1 were analyzed in Burmese and Karen groups residing in Thailand or on the Thai–Burma border.

The studied population consisted of 370 unrelated healthy Burmese individuals representing two different ethnic groups, including 170 Burmese (residing in Thailand and the Burmese town of Myawaddy on the border with Thailand) and 200 Karen (residing as migrants in Thailand). All samples were collected after informed consents were obtained, and all the participants were interviewed to confirm their ethnic background for at least two generations. DNA samples were extracted by using the guanidine–hydrochloride method (13). The Khon Kaen

University Ethics Committee for human research (HE490604) approved the study.

The HLA class I and class II alleles were genotyped by the method polymerase chain reaction sequence-specific primer (PCR-SSP) method (14). Allele-specific primers were designed based on single-nucleotide polymorphism of published nucleotide sequences in the IGMT/HLA database (15). Most of the allele-specific primers presented at the 12th International Histocompatibility Workshop (16) were used in this study for genotyping at the low- to high-resolution levels but are reported here at the field one or two level of resolution for consistency. Because particular alleles could have the same SSP pattern, the group names were designated based on the lowest allele number and a suffix 'g' to denote the cluster of alleles (Table S1, Supporting Information). For example, the assignment of *A*02:01g* includes *A*02:01*, *04*, *06–07*, *09–11*, *14–18*, *20–21*, *26*, *29–33*, *36, 39–43*, *45*, *51–53*, *57–61*, *64*, *66–75*, *77* and *79–90* alleles. Samples exhibiting rare alleles or ambiguous SSP patterns were subjected to direct DNA sequencing or the Luminex-SSO method (17) to clarify their assignments.

The allele frequency distributions of HLA class I and class II loci in Burmese and Karen populations residing in Thailand are presented in Table 1. The number of HLA-A, -B, -C, -DRB1 and -DQB1 alleles detected in Burmese was 15, 32, 19, 15 and 15, respectively and 13, 27, 17, 15 and 11 in Karen, respectively. Some or all these numbers may be an underestimate if the PCR-SSP primers have not detected some specific alleles. Hardy–Weinberg analysis revealed that all the HLA loci were in equilibrium except for HLA-C and HLA-DQB1 in the Burmese (Table S2). The disequilibrium at two HLA loci in Burmese may have been caused by PCR genotyping errors such as allele drop out, resulting in the large number of designated blanks, 'null alleles', for HLA-C (10.9%) and HLA-DQB1 (8.2%), possibly leading to a false observation of an excess of homozygotes. Alternatively, other factors may have been responsible for the disequilibrium, such as affects of overdominant or balancing selection favoring an excess of homozygotes or heterozygotes.

The Burmese and Karen populations are significantly different from each other based on the fixation index (Fst) pairwise population measures, different indexes of dissimilarities and the exact test of population genic differentiation (Table S3). Also, the chi-squared test was used to determine the differences between the allele frequencies in Burmese and Karen (Table 1) and in different Asian populations (Table S4 and S5). Of the 43 HLA-lineage allele frequencies that were matched between Burmese and Karen, significant differences (P-corrected < 0.05) were obtained for 12 (27.9%), that is, for *A*11*, *A*33*, *B*15*, *B*35*, *B*44*, *C*04*, *DRB1*07*, *DRB1*10*, *DRB1*11*, *DRB1*15*, *DQB1*05* and *DQB1*06*. This relatively low number of significant differences suggests that the Burmese and Karen are more genetically related to each other and the Thai than to many other Asian ethnic groups (Table S4 and S5).

*A*11* is one of the most common and highly prevalent HLA-A alleles in Southeast Asians (18, 19). The *A*11:01g* allele was the highest HLA-A allelic frequency in both the Burmese (24.1%) and the Karen (34.3%), although it was significantly different in frequency between the two populations. High frequencies of *A*11* were previously found in Thais (32.5% and 28.9%), Khin in Vietnam (26.7%), Chinese Han in Hong Kong (33.8%) and Han in China (29.4%) (Table S4).

The two most common *B*15* alleles detected in Burmese and Karen were *B*15:02g* and *B*15:20g*, respectively. Most of the *B*15* in Burmese were *B*15:02*, *B*15:32* and *B*15:25* (20). A marked difference was found in *B*15* allele frequencies between the Burmese and the Karen and between the Burmese and other Asians including the Taiwanese, Koreans, Japanese, North Indians, Sinhales in Sri Lanka, Sindhi in Pakistan and Turks (Table S4). In contrast, there was no significant difference between the Burmese and the Bangladeshis, the Thais, Vietnamese or the Chinese from Singapore, Hong Kong and China (Table S4). This observation is consistent with previous findings that the prevalence of *B*15:02g* was high in some Asian populations, but low in Japanese, Koreans, Sri Lankan and Caucasians (21). The frequency of *B*15:20g* was approximately seven times higher in Karen (17%) than in Burmese (2.1%), whereas there was no significant difference between the Karen and Burmese for the other nine *B*15* alleles (Table 1).

A strong association between *B*15:02* and carbamazepine (CBZ)-induced Steven-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in Han Chinese, Malaysian and Thais (6, 21–24). Studies from Europe showed that *B*15:02* is not a specific marker for CBZ-induced SJS/TEN but is ethnicity specific for Asians. Furthermore, the incidence of SJS/TEN is not known in many ethnic Asians, such as Filipinos, Indonesians, Pakistanis, Laotians, Cambodians and Burmese. Therefore, the determination of the prevalence of *B*15:02* in these ethnic groups is of high priority for a better understandings of its association with CBZ-induced SJS/TEN. Because *B*15:02g* was present at a high frequency in Karen (12.4%) and Burmese (8.8%), further studies are warranted to determine the prevalence of SJS/TEN and the association between *B*15:02* and CBZ-induced SJS/TEN in these two ethnic groups.

The significant difference in the *B*46* allele frequency between the Burmese (3.5%) and the Thai (14%) populations (Table S4) is an interesting observation given the regular flow of people between the Burmese and Thai borders. The *B*46*-carrying haplotype is apparently more fragmented in Northeast Thais, comprising of seven haplotypes with different HLA-A and HLA-DR/DQ combinations (10).

A marked difference was detected at the HLA-C locus for the *C*04* allele frequency between Karen (27%) and most of the other populations used in this comparison (Table S4). This allele was highly associated with *B*15:20g*, which at 17% predominated the other HLA-B alleles in the Karen. A high frequency of *C*08* was found in Southeast Asians (Thais,

Table 1 Allele frequencies of HLA class I and class II in 170 Burmese and 200 Karen[a]

	AF (%)			AF (%)			AF (%)	
HLA allele	Burmese	Karen	HLA allele	Burmese	Karen	HLA allele	Burmese	Karen
*HLA-A**			*HLA-B**			*HLA-DRB1**		
01	6.5	3.1	*07*	5.3	2.8	*01*	0.6	0.3
02:01g	10.3	3.3	*08*		0.3	*03*	2.7	3.8
02:03	7.6	**12.8**	*13*	4.7	8.6	*04*	7.9	**11.3**
03	1.5	0.5	*14*	0.6	1.0	*07***	12.4	5.0
11:01g*	**24.1**	**34.3**	***15****	**19.5**	**36.1**	*08:03g*	0.6	2.5
24:02g	**16.8**	**19.3**	*15:01g*	1.5	2.8	*09*	2.9	1.5
24:07,19		0.3	***15:02g***	**8.8**	**12.4**	*10***	3.2	0.3
26	1.2	1.8	*15:08*	0.6		*11***	7.1	1.0
29	0.6		*15:12*	0.3		*11:01g*	6.8	1.0
30	0.3	0.3	*15:13*	0.9	1.8	*12*	16.8	19.6
31	2.6	0.8	*15:16g*		0.3	***12:02g***	**15.3**	**19.3**
33**	**13.8**	5.3	*15:17*	0.6		*13*	2.4	1.8
34		0.3	*15:21*	0.9		*13:01g*	2.1	1.5
36	0.3		***15:20g***	2.1	**17.0**	*14*	6.1	3.9
66	0.3		*15:32*	3.5	1.8	*14:01g*	3.5	2.8
68	3.2	1.3	*18*	1.5	0.5	*14:04g*	2.6	0.8
74	0.3		*27*	1.8	1.1	*15***	28.8	37.8
Blank	10.6	17.3	*35***	8.2	3.3	***15:01g***	**14.1**	**27.0**
HLA-C*			*35:01g*	3.8	2.8	***15:02g***	**14.4**	**10.5**
01	5.6	8.0	*35:05g*	4.4		*16*	0.6	1.8
02	0.3	0.3	*37*	2.1	2.3	Blank	7.9	10.0
03:02	3.8	3.5	*38*	5.6	2.0	***HLA-DQB1****		
03:03g	1.8	2.5	*39*	0.9	2.3	***02***	**11.2**	7.5
03:04g	2.9	2.5	*40*	5.5	5.8	*03*	33.0	27.6
*04***	14.2	27.1	*40:01g*	2.6	3.0	***03:01g***	**20.9**	**16.8**
04:01g	**12.1**	**20.0**	*40:02g*	2.9	2.8	*03:02g*	4.7	8.5
04:04g	1.8	7.1	*44***	10.6	4.1	*03:03,15*	5.6	2.0
05	0.6	1.3	***44:02g***	**10.3**	3.8	*04:01*	0.6	3.0
06:02g	5.3	3.3	*46*	3.5	1.3	*04:02*	0.3	
07	27.7	17.6	*48*	1.2		*05***	33.0	42.3
07:01g	9.7	2.5	*51*	7.1	2.8	***05:01***	**11.2**	**10.0**
07:02g	**15.3**	**14.5**	***52***	**8.2**	**9.1**	***05:02***	**15.0**	**29.0**
07:03g	0.3		*54*	0.3		*05:03*	6.2	2.8
07:04g	1.2	0.3	*55*	0.9	0.8	*05:04*	0.3	0.5
08	**11.8**	**15.3**	*56*	2.1	6.5	*06***	13.9	6.3
12:02g	4.7	2.5	*57*	3.5	0.9	*06:01*	10.3	4.5
12:03g	4.4	1.5	*58*	3.5	3.8	*06:02g*	0.9	
12:05g	0.3	0.6	*67*		0.3	*06:03g*	1.8	
15	5.6	3.6	*81*	0.3		*06:04g*	0.6	
16:02	0.3		Blank	3.5	5.5	*06:05g*	0.3	1.8
Blank	10.9	10.8				Blank	8.2	12.5

AF, allele frequency; HLA, human leukocyte antigen.

[a]High frequency in Burmese or Karen are given in bold.

** *P*-corrected <0.05 between Burmese and Karen.

Vietnamese, Malaysian and Burma) and Eastern Asians (Taiwanese, Chinese, Korean and Japanese), but at lower frequently in Southern Asians (Turks, Pakistan, Indian and Sri Lankan) (Table S4).

*HLA-DRB1*12* is commonly observed in all Southeast Asian populations (25–29). The *DRB1*12* allele frequency in the Karen and the Burmese was similar to those in Thais, and much higher than in the Sinhalese, Sindhi in Pakistan, Turks, Japanese and Koreans (Table S5). The frequency of *DRB1*15:01g* (27%) was higher than *DRB1*15:02g* (10.5%) in Karen, but at a similar frequency of 14% in the Burmese (Table 1). A high frequency of *DRB1*15* was observed also in Thais, along with marked differences between Burmese and Karen, Vietnamese, Turks, Timorese, Filipinos, Taiwanese, Chinese, Koreans and Japanese (Table S5). Although the distribution of HLA class II alleles in Central and Northeast Thailand and Southern Chinese populations were similar, the distribution in the Central Thais was a mixture of those in Southern and Northeast Chinese,

Table 2 Significance of genotypic linkage disequilibrium for each HLA locus pair in Karen and Burmese[a]

	HLA loci				
Pop	Locus 1	Locus 2	*P*-value	SE	Switches
Karen	A	B	0.00000	0.000000	519
Karen	A	C	0.00325	0.003250	1103
Karen	B	C	0.00431	0.004310	301
Karen	A	DQ	0.00000	0.000000	1046
Karen	B	DQ	0.01266	0.009389	298
Karen	C	DQ	0.00000	0.000000	743
Karen	A	DR	0.06167	0.017399	3673
Karen	B	DR	0.00009	0.000090	1586
Karen	C	DR	0.00000	0.000000	2948
Karen	DQ	DR	0.00000	0.000000	2824
Burmese	A	B	0.11128	0.030980	207
Burmese	A	C	0.09547	0.029108	781
Burmese	B	C	0.02605	0.015236	245
Burmese	A	DQ	0.08994	0.023684	634
Burmese	B	DQ	0.08137	0.026763	198
Burmese	C	DQ	0.31151	0.044609	724
Burmese	A	DR	0.08050	0.020111	3454
Burmese	B	DR	0.00000	0.000000	1521
Burmese	C	DR	0.02006	0.005927	4484
Burmese	DQ	DR	0.00000	0.000000	3580

HLA, human leukocyte antigen; SE, standard error.

[a]GENEPOP v4.2 analysis (http://genepop.curtin.edu.au) using the log likelihood ratio statistic in the Linkage Disequilibrium (Option 2) test for each pair of loci in each population with the following Markov chain parameters default settings: Dememorization: 1000; Batches: 100; Iterations per batch: 1000.

suggesting the existence of Thai–Chinese admixtures in the Central Thai population (27).

The most frequent alleles in the Karen and Burmese at the HLA-DQB locus were the *DQB1*03* and **05* groups; and the *DQB1*05:02* allele predominated over *DQB1*05:01* (Table 1). The frequencies of *DQB1*05* in Karen and Burmese were similar to those previously found in Southeast Asians but were lower than those in Eastern and Northern Asians (Table S5). In contrast, the frequencies of *DQB1*06* were lower in Karen and Burmese and in other Southeast Asian populations than in Eastern and Northern Asians. Thus, the frequencies of *DQB1*05* and *DQB1*06* appear to differentiate the Southeast Asians from the Eastern and Northern Asians.

The frequencies of HLA-C1/C2 and HLA-Bw4/Bw6 ligand groups in different populations are of interest because these groups interact with killer cell immunoglobulin-like receptors (30). Table S6 shows the frequency of the HLA-C1/C2 and HLA-Bw4/Bw6 ligand groups in the Karen and Burmese.

The linkage disequilibrium (LD) for each locus pair was highly significant ($P < 0.05$, Fisher's method) across the Karen and Burmese populations (Table S7). However, Table 2 shows that the genotypic LD inferred for each locus pair using the Markov chain parameters (31) in the Genepop computer software, v4.2 (http://genepop.curtin.edu.au) was more significant ($P < 0.05$) in Karen (9 of 10 paired loci) than in Burmese (4 of 10 paired loci). The permutation test using an Expectation-maximization (EM) algorithm (32) in the Arlequin software package (33) revealed the same trend but was even more significant at $P < 0.05$ with all 10 paired loci in LD in Karen and 8 of 10 paired loci in LD in the Burmese with only the HLA-A and -C paired loci and HLA-A and -DQB not in LD ($P > 0.05$). The two-locus haplotype frequencies in the Karen and Burmese are listed in Table S8. The four predominant two-locus haplotypes in Karen were *A*11:01g-B*15:20g* (14.5%), *B*15:20g-C*04:01g* (14.5%), *B*15:20g-DRB1*15:01g* (14.8%) and *DRB1*15:01g-DQB1*05:02* (22.3%). Although the *DRB1*15:02g-DQB1*05:01* haplotype was present at low frequency in Karen (9.5%), it has been strongly associated with systemic lupus erythematosus (SLE) in Thais and Taiwanese (34, 35). In addition, the *DRB1*15:02-DQB1*05:01* haplotype is considered to be the major HLA haplotype conferring susceptibility to SLE in Southeast Asian population, pointing to the importance of investigating this haplotype in Karen SLE patients.

The three-locus haplotype frequencies for A-B-C and A-B-DRB1 in the Burmese and Karen are shown in Table S9. The two most common three-locus haplotypes were *A*11:01g-C*04:01g-B*15:20g* (12.3%) and *A*11:01g-B*15:20g-DRB1*15:01g* (12.8%). In a comparison between the Burmese and Karen for the three-locus haplotype frequencies, eight were statistically significant at *P*-corrected < 0.05 (Table S9), whereby five were higher in Karen than Burmese, and three were higher in Burmese than in Karen.

The most common five-locus haplotype in Karen was *A*11-C*04-B*15:20g-DRB1*15:01g-DQB1*05:02* (10.3%). Many of the Burmese and Karen HLA haplotypes reconstructed in this study were also found in Thais, Vietnamese and other Asian populations. However, we found a significant difference in the five-locus haplotype frequency of *A*33-C*03:02-B*58-DRB1*03-DQB1*02* between the Burmese and Karen and the Northeast Thais (10), Thais-Chinese (11), Khin (26) and Singaporian Chinese (36). The *B*58-DRB1*13* haplotype (1.8%) was present in Karen, but not in the Burmese; whereas *B*58-DRB1*03* (1.8%) was present in Burmese, but not in the Karen (Table S8). In this regard, *A*33-B*58-DRB1*13* was ranked as the fourth most frequency (1.9%) in the Jiangsu Han of China (37).

According to Di and Sanchez-Mazas (2, 38), there are group 1 and group 2 HLA lineages and alleles that belong more frequently or exclusively to the North East Asian (NEA) (China, Mongolia, Korea and Japan) and South East Asian (SEA) populations, respectively. For example, *A*01*, *A*03*, *A*24*, *B*35*, *B*44*, *B*52*, *DRB1*04* and *DRB1*7* belong to group 1 (NEA), whereas *A*11*, *B*15*, *C*01*, *C*08*, *DRB1*12*, *DRB1*14*, *DRB1*15* and *DRB1*16* belong to group 2 (SEA) (2). In our study (Table 1, Tables S4 and S5), 10 of the 24

(41.7%) top-three most frequent HLA lineages at four loci (A, B, C and DRB1) belong to the SEA, group 2. On the other hand, 6 of the 24 (25%) top-three most frequent HLA lineages at 4 loci (A, B, C and DRB1) belong to the NEA, group 1. The other eight (33.3%) lineages could belong to either group. Many of the so-called SEA lineage alleles, like *A*11*, *B*15*, *C*8* and *DRB1*15,* are also present at relatively high or moderate frequency in Chinese Han, Japanese and Koreans (Tables S4 and S5). Thus, these comparisons suggest that the Burmese and Karen have had a relatively high level of admixture with non-Han and Han from NEA. Whereas the Burmese and Karen HLA lineage and allele frequencies are consistent with an 'overlapping model' for their migratory history, we cannot conclude from these findings whether the gene flow of the Burmese and Karen was mainly from the northern or southern migratory routes that were hypothesized by Di and Sanchez-Mazas (2, 38). For a study of population genetic relationships and migration models, more detailed analyses of each HLA locus and combined loci are required to compare the Burmese and Karen with other Asian and non-Asian populations, but clearly, such analyses are beyond the scope of this brief communication.

In conclusion, this study provides the first HLA class I and class II genotyping results in Burmese and Karen populations. We presented the common low-resolution alleles and haplotypes found in these two ethnic groups. In a comparison with other Asian populations, the Burmese and Karen appear to be genetically distinct but closer to each other than to the other South Asian populations in terms of HLA allele and haplotype frequencies. This study will be useful as a starting point for further studies in anthropology, organ transplantation and the association between HLA allele and disease or drug hypersensitivity in Burma and Thailand.

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Conflict of interest

The authors have declared no conflicting interests.

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Supporting Information

The following supporting information is available for this article:

Table S1. The abbreviations of allele groups

Table S2. HLA loci H-W exact test

Table S3. Population differentiation and Fst indices for Karen and Burmese at HLA loci

Table S4. Comparison of HLA class I alleles between Burmese, Karen and 19 other populations

Table S5. Comparison of HLA class II alleles between Burmese, Karen and 19 other populations

Table S6. HLA ligands for KIR in the two populations (%)

Table S7. *P*-value for each locus pair across the two populations (Fisher's method)

Table S8. List of two-locus haplotypes in Burmese ($N = 170$) and Karen ($N = 200$)

Table S9. Three-locus haplotype frequencies in 170 Burmese and 200 Karen populations (%HF > 1.0)