Distribution of HLA Class I Alleles and Haplotypes in Korean

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The antigen (phenotype), gene (allele) and haplotype frequencies of HLA class I were analysed in 4,622 Koreans. With allele frequencies of over 0.05, the most frequent HLA-A,-B and -C antigens were A2, A24, A33, A11, A26, A31; B62, B51, B44, B54, B61, B35, B58, B60; Cw3, Cw1, Cw4, Cw7. Of these A2, A24, Cw1 and Cw3 were present in very high frequencies, respectively (0.3211, 0.2200, 0.2204, and 0.3737). The most common haplotypes with frequencies larger than 0.02 were A2-Blank, A33-B44, A33-B58, A11-B62, A24-B51, A24-B54, A2-B27, B54-Cw1, B58-Cw3, B51-Blank, B61-Cw3, B62-Cw4, B35-Cw3, B44-Blank, B60-Cw3, B27-Cw1, A2-Cw3, A2-Cw1, A24-Cw1, A33-Cw3, A26-Cw3, and A11-Cw4. A significant negative linkage disequilibrium was found for the haplotypes of A2-B7, A2-B44, A2-B58, A24-B13, A24-B27, A33-B54 and A33-B62, of which frequencies were larger than 0.003. The B-C and A-C haplotypes which showed the significant negative linkage disequilibrium were B44-Cw1, B51-Cw1, B44-Cw3, B62-Blank, A2-Cw4, A2-Blank, A11-Cw3, A11-Blank and A33-Cw1 and had frequencies higher than 0.01. The findings presented here could be used per se to estimate the populational relationships or as the control data for HLA-disease investigation. Furthermore they could provide the scope for the definition of new antigens.

Key Words: *HLA class I, allele and haplotype frequencies*

INTRODUCTION

Korea is a peninsula located between China and Japan, and surrounded by the Pacific Ocean to the east, and the Yellow Sea to the west and the Straits of Korea to the south. It has a population of nearly sixty six million. The Korean people are believed to be originally derived from Mongolians, who migrated to the Korean Peninsula about five thousand years ago, and preserved many of the physico/anthropological characteristics of Mongolians. Through ancient history, Korea had much contact with China and Japan in the aspects of culture, religion and agriculture and it is evident that the three countries have very similar literature, customs and clothes, etc. Cultural, archeological and linguistic studies could partially reveal the origins of these cultures. It is hoped that genetic studies would help to resolve this issue, especially using a multigenic, polymorphic system such as HLA which is unchangeable by social customs and culture. It is well known that each major race of the world is characterized by a high or low frequency of a specific antigen and by certain HLA haplotypes (Bauer and Danilovs, 1980). Therefore, finding out how close the HLA pattern of Koreans to other related countries by populational data is an interesting study.

The major histocompatibility complex, a well-defined system in humans known as HLA, is a set of loci on the short arm of chromosome 6 which determines the fate of transplantation, plays a role in the control of cel-

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lular interactions responsible for immune responses, and appears to be associated with a variety of diseases. The HLA region consists of clusters of genes known as class I, class II, and class III. The region (class III) between class I and class II is a stretch of DNA which has genes coding for complements, tumor necrosis factors, heat shock proteins, and other molecules whose functions are not yet known (Trowsdale et al., 1991). The genes of the class I region code for the HLA -A, -B, -C antigens, and those of the class II region code for DR, DQ, and DP molecules. Class I genes are highly polymorphic; the A, B, and C loci contain 23, 48, and 9 alleles, respectively. The DR, DQ,

and DP genes are less polymorphic (Bodmer et al., 1992).

HLA alleles are codominantly inherited. The high degree of polymorphism and codominant inheritance make HLA antigens the ideal genetic markers for disease. Population studies of the HLA system provide information about the genetic differences between populations and the linkage between hypothetical disease susceptible genes and immune response genes or other genes of the HLA system. Furthermore, comparison by disease association in different racial and ethnic groups may provide significant information about the genetic mechanisms involved in susceptibilty

Table 1. Phenotype and allele frequencies of HLA-A,-B,-C in Koreans (n=4,622).

Antigen	PF	GF	SD	Antigen	PF	GF	SD
A 1	0.0376	0.0190	0.0014	B 7	0.0636	0.0323	0.0018
A 2	0.5392	0.3211	0.0048	B 8	0.0108	0.0054	0.0007
A 3	0.0253	0.0127	0.0011	B13	0.0872	0.0446	0.0021
A11	0.2038	0.1077	0.0032	B14 (64, 65)	0.0130	0.0065	0.0008
A24 (9)	0.3916	0.2200	0.0043	B27	0.0742	0.0378	0.0019
A26 (10)	0.1140	0.0587	0.0024	B35	0.1209	0.0624	0.0025
A30 (19)	0.0591	0.0300	0.0017	B37	0.0247	0.0124	0.0011
A31 (19)	0.1103	0.0568	0.0024	B38 (16)	0.0117	0.0059	0.0007
A33 (19)	0.2283	0.1215	0.0033	B39 (16)	0.0318	0.0160	0.0013
Other*	0.0169	0.0084	0.0009	B44 (12)	0.1458	0.0758	0.0027
A-Blank		0.0441	0.0021	B46	0.0273	0.0137	0.0012
				B47	0.0024	0.0012	0.0003
				B48	0.0402	0.0203	0.0014
				B51 (5)	0.1685	0.0882	0.0029
				B52 (5)	0.0290	0.0146	0.0012
				B53	0.0089	0.0044	0.0006
				B54 (22)	0.0344	0.0174	0.0013
				B55 (22)	0.1489	0.0774	0.0027
				B56 (22)	0.0113	0.0056	0.0007
Antigen	PF	GF	SD	B57 (17)	0.0050	0.0025	0.0005
Cw1	0.3923	0.2204	0.0043	B58 (17)	0.1138	0.0586	0.0024
Cw2	0.0190	0.0096	0.0010	B59	0.0331	0.0167	0.0013
Cw3 (9, 10)	0.6077	0.3737	0.0050	B60 (40)	0.1119	0.0576	0.0024
Cw4	0.1255	0.0648	0.0025	B61 (40)	0.1257	0.0650	0.0025
Cw5	0.0024	0.0012	0.0003	B62 (15)	0.2428	0.1298	0.0034
Cw6	0.0149	0.0075	0.0008	B67	0.0056	0.0028	0.0005
Cw7	0.0898	0.0459	0.0021	B75 (15)	0.0407	0.0205	0.0014
Cw8	0.0052	0.0026	0.0005	Other**	0.0067	0.0035	0.0007
C-Blank		0.2743	0.0046	B-Blank		0.1011	0.0031

* Other comprise A29, A32, A34, A66 and A69.
** Other comprise B18, B21, B41, B42, B63, B73, B76, B77 and B78.
PF=Phenotype or Antigen Frequency
GF=Gene or Allele Frequency
SD=Standard Deviation

Table 2. The frequencies of HLA-A and -B haplotypes with the significant positive linkage disequilibrium (delta).

Haplotype	Frequency	Delta	chi-square
A 1-B37	0.00777	0.00753	1138.08
A 1-B57	0.00073	0.00068	45.38
A 2-B27	0.02038	0.00824	31.77
A 2-B46	0.00860	0.00420	22.31
A 2-B48	0.01214	0.00562	27.17
A 2-B75	0.01122	0.00464	18.30
A 2-Blank	0.04772	0.01526	31.54
A 3-B 8	0.00136	0.00129	112.84
A 3-B21	0.00021	0.00020	16.40
A 3-B27	0.00200	0.00152	22.64
A 3-B44	0.00320	0.00224	25.25
A 3-B78	0.00011	0.00011	38.51
A11-B39	0.00394	0.00222	14.09
A11-B62	0.03125	0.01727	113.93
A11-B67	0.00136	0.00106	18.05
A24-B 7	0.01479	0.00768	44.24
A24-B51	0.02966	0.01026	29.91
A24-B52	0.00945	0.00624	63.95
A24-B54	0.02370	0.00667	14.24
A24-B59	0.00916	0.00549	43.34
A24-B60	0.01963	0.00696	20.66
A26-B35	0.00733	0.00407	22.29
A26-B61	0.01052	0.00670	58.43
A29-B 7	0.00248	0.00238	271.62
A29-B42	0.00011	0.00011	53.40
A30-B13	0.01504	0.01370	683.34
A30-B14	0.00450	0.00431	449.33
A31-B51	0.01253	0.00752	56.70
A31-B61	0.00674	0.00305	12.43
A32-B44	0.00145	0.00128	45.94
A33-B44	0.04661	0.03740	813.08
A33-B58	0.04108	0.03396	854.82
A66-B44	0.00054	0.00050	29.32
A69-B63	0.00010	0.00010	27.09
Blank-Blank	0.01632	0.01186	37.15

to HLA-associated diseases (Tiwari and Terasaki, 1985).

Although a few studies of the HLA antigen distribution in Korea have been published by our group and others, only a few hundred persons were subjects in the previous studies (Han et al., 1986). In this paper, we report the HLA -A, -B, -C antigen, gene and haplotype frequencies in 4,622 Koreans. Because of the large number of subjects, we could detect larger numbers of the significant haplotypes and we found rare antigens. This study has been conducted since 1980.

MATERIALS AND METHODS

Subjects

In the past 13 years, blood samples have been collected from 4,622 healthy, unrelated adult Koreans. The volunteers consisted mainly of both teaching and non-teaching staff, and students from our medical college.

HLA-A, -B, -C Typing

Lymphocytes were isolated from heparinized blood by density gradient centrifugation on Ficoll-Hypaque. HLA -A, -B, -C typing was done according to the standard microlymphocytotoxicity technique (Terasaki et al., 1974) using trays obtained partly from commercial sources and partly from our laboratory. For HLA specificities, we followed the standard nomenclatures of the HLA alleles (Bodmer et al., 1992). However, we made a few modifications when split specificities could not be clearly separated. In practice, we included B64 and B65 into B14, B49 and B50 into B21, Cw9 and Cw10 into Cw3. The anti-sera for the following specificities were recently used: A29, A32, A34, A66, A69, B18, B21, B41, B42, B63, B73, B76, B77 and B78. Anti-sera specific for A23, A36, A43, A68, A74 and B70 (B71, B72) were not used in this study.

Statistical Analysis

The results were analysed using programmes developed by our group in dBASE III-Plus. Under the assumption of the Hardy-Weinberg equilibrium, the

Table 3. The frequencies of HLA-A and -C haplotypes with the significant positive linkage disequilibrium (delta).

Haplotype	Frequency	Delta	chi-square
A 1-Cw6	0.00085	0.00071	16.65
A 2-Cw1	0.09583	0.02506	57.53
A 2-Cw3	0.13414	0.01414	11.66
A 3-Cw2	0.00186	0.00174	116.80
A11-Cw4	0.02275	0.01577	183.19
A24-Cw1	0.06100	0.01251	19.21
A26-Cw3	0.03099	0.00905	22.21
A29-Cw2	0.00030	0.00027	11.71
A30-Cw6	0.00290	0.00268	151.52
A30-Cw8	0.00093	0.00085	43.33
A30-Blank	0.01322	0.00499	10.65
A32-Cw5	0.00021	0.00021	76.61
A33-Cw3	0.06050	0.01510	31.21
A66-Cw2	0.00021	0.00021	38.90
A69-Cw4	0.00112	0.00098	32.99

Table 4. The frequencies of HLA-A and -C haplotypes with the significant positive linkage disequilibrium (delta).

Haplotype	Frequency	Dalta	chi-square
B 7-Cw7	0.01157	0.01009	333.34
B 8-Cw8	0.00156	0.00131	32.78
B13-Cw6	0.00318	0.00285	115.38
B14-Cw8	0.00086	0.00084	193.23
B21-Cw5	0.00011	0.00011	50.75
B27-Cw1	0.02438	0.01605	167.06
B27-Cw2	0.00630	0.00594	464.20
B35-Cw3	0.04258	0.01926	96.41
B35-Cw4	0.00735	0.00331	13.37
B37-Cw6	0.00078	0.00069	24.26
B38-Cw7	0.00200	0.00173	52.63
B39-Cw7	0.00519	0.00446	129.43
B41-Cw8	0.00021	0.00021	92.98
B44-Cw5	0.00107	0.00098	51.57
B44-Cw7	0.01087	0.00739	77.75
B44-Blank	0.03862	0.01783	56.56
B46-Cw1	0.01136	0.00834	121.47
B46-Cw3	0.00938	0.00426	20.42
B51-Blank	0.04899	0.02480	96.11
B52-Blank	0.00868	0.00468	19.02
B54-Cw1	0.06905	0.05199	918.75
B55-Cw1	0.01137	0.00754	78.59
B56-Cw1	0.00354	0.00231	22.49
B57-Cw6	0.00042	0.00040	39.73
B58-Cw3	0.05271	0.03081	267.24
B59-Cw1	0.01489	0.01121	181.41
B60-Cw3	0.03794	0.01641	75.31
B61-Cw3	0.04336	0.01907	90.87
B62-Cw4	0.04306	0.03465	760.03
B67-Cw7	0.00225	0.00212	164.89
B75-Cw3	0.01183	0.00417	13.11

Table 5. Two-locus haplotype frequencies of HLA class I with the significant negative linkage disequilibrium (delta).

Haplotype	Frequency	Delta	chi-square
HLA-A and -B Haplotypes			
A 2-B 7	0.00582	-0.00455	11.07
A 2-B44	0.00643	-0.01791	73.30
A 2-B58	0.00382	-0.01500	66.25
A11-B44	0.00126	-0.00690	29.35
A11-B58	0.00125	-0.00506	20.32
A24-B13	0.00401	-0.00580	18.09
A24-B27	0.00408	-0.00424	11.36
A24-B44	0.00260	-0.01408	62.98
A24-B58	0.00161	-0.01128	51.99
A33-B35	0.00197	-0.00561	20.96
A33-B51	0.00178	-0.00894	37.96
A33-B54	0.00404	-0.00536	15.54
A33-B62	0.00535	-0.01042	35.71
HLA-A and -C Haplotypes			
A 1-Cw3	0.00202	-0.00508	20.70
A 2-Cw4	0.01038	-0.01043	29.25
A 2-Blank	0.06261	-0.02547	27.88
A11-Cw3	0.02365	-0.01660	39.93
A11-Blank	0.01938	-0.01016	12.36
A30-Cw1	0.00186	-0.00475	17.88
A30-Cw3	0.00586	-0.00535	14.61
A33-Cw1	0.01486	-0.01192	28.65
A33-Cw4	0.00227	-0.00560	20.11
HLA-B and -C Haplotypes			
B 7-Cw1	0.00117	-0.00595	26.02
B13-Cw1	0.00164	-0.00819	35.86
B39-Cw3	0.00222	-0.00376	13.42
B44-Cw1	0.01017	-0.00654	13.71
B44-Cw3	0.01325	-0.01508	46.09
B51-Cw1	0.01293	-0.00651	11.73
B54-Blank	0.00550	-0.01573	40.13
B55-Cw3	0.00233	-0.00417	15.26
B61-Cw1	0.00883	-0.00550	11.24
B62-Blank	0.02035	-0.01525	23.11

gene frequencies (p) were calculated from the antigen frequencies (a) by Bernstein's formula: $p = 1 - \sqrt{(1-a)}$, where $a = n/N$, and n represents the number of individuals expressing the phenotype in a sample of N randomly selected individuals. The frequency of the 'blank' gene was obtained by subtracting the sum of defined gene frequencies from 1. The standard deviation (SD) of allele frequency was calculated as $SD = \sqrt{[p(1-p)/2N]}$ (Pickbourne et al., 1978)

Haplotype frequencies (HF) and linkage disequilibrium (LD) between alleles of the given two loci were estimated according to Mattiuz et al (1970): $LD = \sqrt{(d/N)} - [\sqrt{(b+d)}(c+d)]/N$ where a, b, c, and d are $++$, $+-$, $-+$, and $--$ for each combination and N is the total number of persons under study.

Haplotype frequencies were obtained $p^{AB} = p^A \times p^B + LD$. P^A and p^B are the genotypes for the given antigens in each combination. The significance of LD values was recorded by the 2×2 chi-square test.

RESULTS

HLA-A, -B and -C antigens

Table 1 shows the phenotype and allele frequen-

cies of the HLA-A, -B and -C locus antigens in 4,622 Koreans. The most frequent antigens of the HLA-A, -B and -C, with allele frequencies of over 0.05, were; A2, A24, A33, A11, A26, A31; B62, B51, B44, B54, B61, B35, B58, B60; Cw3, Cw1, Cw4, Cw7. Of them, A2, A24, Cw1 and Cw3 were present in high frequencies, respectively (0.3211, 0.2200, 0.2204 and 0.3737). The somewhat rare HLA-A and -B locus antigens were recently detected by using our placenta anti-sera: A29, A32, A34, A66, A69; B18, B21, B41, B42, B63, B73, B76, B77, B78. The HLA-A25, B45 were not found in this study. The frequency of blank alleles in the HLA-C locus was high (0.2743) while that of the HLA-A and -B loci were low (0.0441 and 0.1011, respectively).

Two-locus haplotypes

The estimated haplotype and the significant linkage disequilibrium values for HLA-A and -B; HLA-A and -C; HLA-B and -C, are presented in table 2, 3, and 4. The haplotypes with the positive and negative linkage disequilibrium are statistically significant at the 0.1% level.

The most common A-B haplotypes with frequencies larger than 0.02 were A2-Blank; A33-B44; A33-B58, A11-B62; A24-B51; A24-B54 and A2-B27. The most common B-C haplotypes were B54-Cw1, B58-Cw3, B51-Blank, B61-Cw3, B62-Cw4, B35-Cw3, B44-Blank, B60-Cw3 and B27-Cw1. And the most common A-C haplotypes were A2-Cw3, A2-Cw1, A24-Cw1, A33-Cw3, A26-Cw3 and A11-Cw4.

A significant negative linkage disequilibrium was found for the haplotypes of A2-B7, A2-B44, A2-B58, A24-B13, A24-B27, A33-B54, and A33-B62, of which the frequencies were larger than 0.003. The B-C and A-C haplotypes which showed the significant negative linkage disequilibrium frequencies larger than 0.01 were B44-Cw1, B51-Cw1, B44-Cw3, B62-Blank; A2-Cw4, A2-Blank, A11-Cw3, A11-Blank, A33-Cw1. Table 5 shows the haplotypes with the significant negative linkage disequilibrium, of which the frequencies are larger than 0.001.

DISCUSSION

This study provides a detailed description of HLA class I polymorphisms in Koreans which can be used per se to estimate populational relationships and migration. The data obtained in this study are very similar to those of the previously published study, although some rare antigens are included (Han et al., 1986). The most frequent antigens of the HLA-A, -B, -C, with allele frequency of over 0.05 are A2, A24, A33, A11,

A26, A31; B62, B51, B44, B54, B61, B35, B58, B60; Cw3, Cw1, Cw4, Cw7. The rare, newly defined antigens were recently detected using our placenta antisera. It is well known that some HLA antigens are restricted to some populations (Bauer and Danilovs, 1980). According to the geographical distribution, the HLA antigens can be classified into 6 groups; those are tentatively designated as pan-ethnic, the North Mongoloid, the South Mongoloid, Caucasoid, Negroid, and Oceanoid antigens (Wakisaka et al., 1986). The North Mongoloid antigens are preferentially found in Mongoloids settled in North-East Asia such as Korea, Japan, and China. For example, HLA-B54 is only observed in the Korean, Japanese, and Chinese populations, but it is not present or extremely rare in other Mongoloids. The most interesting antigen is B59 which is only observed in Koreans, Japanese, South Indians and Sourastrans. Several HLA antigens originated in Caucasoids such as A1, A3, A32, B8, B14, Cw5 and Cw6 are rarely found in Korean. The HLA-A25, B45 were not found and the some antigens such as A23, A36, A43, A68, A74, and B70 (B71, B72) were not tested.

Table 2, 3 and 4 shows the two-locus haplotypes with associations which are nominally significant at the $p < 0.001$ level. Even with this significant level, these associations, have to be considered cautiously unless they are supported by the results from independent estimations.

Because of this conservative statistical procedure chi square values are not calculated from some haplotypes possessing one or more alleles with very low frequencies. Most of all associations published as significant frequency on the $p < 0.001$ level in this study can be found, whereas the associations with a level of $p < 0.05$ can not always be substantiated, and in some cases the estimation of the association is now negative. Generally, the numerous two-locus associations linked closely to each other are detected. The number of significant positive linkage disequilibriums between A-B, A-C and B-C locus association are 35, 15, and 31, respectively. Because of the large sample size, we could detect more significant haplotypes than in the previous report (Han et al., 1986).

Concerning the defined split specificities, the associations of the respective broad specificity reported previously, provide evidence to support the splitting. For example, B62 split from B15 and is strongly associated with Cw4 wherease B75 is highly associated with Cw3 and not with Cw4. Other exmaples are represented in some statistically significant haplotypes; B17 splits (B57-Cw6, B58-Cw3); A10 splits (A26-Cw3, A66-Cw2); A19 splits (A29-Cw2, A30-Cw6, A30-Cw8,

A30-C Blank, A32-Cw5, A33-Cw3). Other examples of splits with the same association are found in B16 (B38 and B39)-Cw7, B22 (B54, B55, and B56)-Cw1, and B40 (B60 and B61)-Cw3. In other aspects, the monospecific antigen is associated with the various antigens of other loci. Notably, B27 is significantly associated with both Cw1 and Cw2; B35 with Cw3 and Cw4; B44 with Cw5, Cw7, and C Blank; B46 with Cw1 and Cw3; A2 with Cw1 and Cw3; and A30 with Cw6, Cw8 and C Blank. Therefore, these antigens are suggested to have at least two splits.

The negative two-locus associations are generally detected only for haplotypes with relatively high expected frequencies. Many significant negative linkage disequilibriums with frequencies larger than 0.001 are presented in table 5; 13 haplotypes in HLA-A and-B, 9 haplotypes in HLA-A and-C, and 10 haplotypes in HLA-B and-C locus. These data will help to reveal the haplotypes of individuals.

Various mathmetical models and statistical methods have been developed to analyze and interpret the HLA data. But three or more-locus haplotypes are not reliably estimated from the populational analysis and only a few three-locus haplotypes are found. Therefore, we do not present the frequencies of three locus haplotypes in this paper (Piazza., 1975; Karlin and Piazza, 1981; Nijenhuis and D'Amaro, 1985).

The findings presented here also have implications for several areas of HLA research. The data indicate that the Korean populations still provides the scope for definition of new antigens. For example, A24, the most common antigen in Korea is more heterogeneous in the aspect of haplotype analysis. The residual blank gene frequencies of HLA class I, especially C locus, also have merit for further study. With the application of serologic and molecular techniques, new HLA genes or HLA associated markers are continually being discovered. Studies using these markers will provide new information on HLA and disease association and new insights into the genetics and etiology of certain diseases.

The data provided by this study can be used as control frequencies for HLA-disease investigations in Korean. The differences between populations may reflect the evolutionary forces acting on genomes, with possible implications for disease processes. Population studies will provide information about the linkage between hypothetical disease susceptibility genes and immune response genes or other genes of the HLA system.

Furthermore, comparison of disease association in different racial and ethnic groups may provide significant information about the genetic mechanisms involved in susceptibility to HLA-associated diseases. It is because racial variation have significant effects on the strength of disease associations. As an example, approximately 90-95% of ankylosing spondylitis patients from all races are positive for B27. The normal frequency for B27 is about 10% in Caucasians, 4% in Negro and 1.5% in Oriental. Some antigens vary between the races but unlike ankylosing spondylitis they do not show a disease association in all races. There are several diseases in which significant association with antigens of 2 different loci have been found (Tiwari and Terasaki, 1985). These Antigens are also in strong linkage disequilibrium. Therefore, our haplotype data will be helpful for the interpretation of HLA and disease association study.

The results of this study show that populational studies of HLA antigens might continue to provide valuable material to help elucidate all aspects of MHC function.

Acknowledgements

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