



Determination of HLA-A, -C, -B, -DRB1 allele and haplotype frequency in Japanese population based on family study

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Abstract

Key words

allele frequency; family study; haplotype frequency; human leucocyte antigen; Japanese population

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Introduction

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The human leukocyte antigen (HLA) gene family is characterized by extreme degree of genetic polymorphism and linkage disequilibrium (LD). The varieties in polymorphism and LD patterns of HLA gene family show a tendency to be unique in each ethnic group (1, 2). HLA antigens have been known to play an important role in immune responses. In hematopoietic stem cell transplantation (HSCT), HLA matching between donors and recipients lowers the risk of graft rejection and graft-versus-host disease (GVHD) (3, 4). Morishima et al. suggested that the genetic difference derived from HLA haplotype is associated with acute GVHD in allogeneic HSCT (5). Therefore, HLA haplotype cannot be excluded from consideration during donor selection because of potential contribution from proteins encoded by non-HLA genes inherited with HLA genes.

Several studies reported analysis of HLA allele and haplotype frequency data in the Japanese population (6-9). However, these studies failed to present accurate and detailed information due to the haplotypes estimation using software or small sample size, or both. This necessitates developing a method which can produce accurate and detailed gene distribution. The present

The present study investigates the human leucocyte antigen (HLA) allele and haplotype frequencies in Japanese population. We carried out the frequency analysis in 5824 families living across Japanese archipelago. The studied population has mainly been typed for the purpose of transplant, especially the hematopoietic stem cell transplantation (HSCT). We determined HLA class I (A, B, and C) and HLA class II (DRB1) using Luminex technology. The haplotypes were directly counted by segregation. A total of 44 HLA-A, 29 HLA-C, 75 HLA-B, and 42 HLA-DRB1 alleles were identified. In the HLA haplotypes of A-C-B-DRB1 and C-B, the pattern of linkage disequilibrium peculiar to Japanese population has been confirmed. Moreover, the haplotype frequencies based on family study was compared with the frequencies estimated by maximum likelihood estimation (MLE), and the equivalent results were obtained. The allele and haplotype frequencies obtained in this study could be useful for anthropology, transplantation therapy, and disease association studies.

> study aims to obtain a more exact and detailed HLA haplotype distribution from 18,604 members of 5824 Japanese families, whose HLA haplotypes were determined by descent. Our study also attempts to determine the frequency of specific haplotypes, C-B, A-B-DRB1, and A-C-B-DRB1, used in donor search. In addition, it was ascertained whether the haplotype frequencies estimated by maximum likelihood estimation (MLE) would be equivalent to the frequencies found in the present family study.

Materials and method

Subjects

A total of 18,604 members (including patients and normal subjects) from 5824 families, distributed in all parts of Japan, were enrolled for this study. Among these families, there were patients, considered for transplantation, especially HSCT. The families were divided into three groups (Table 1): (i) families with both parents with one or more children, (ii) families with one parent with one or more children, and (iii) families with no parents but having two or more children. The families with more than two generations were counted as separate families. Informed consent was obtained from all the participants of this study by the clinicians who ordered HLA typing.

For comparing the haplotype frequencies obtained by family study and using MLE software, unrelated 4500 people were

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Table 1 Breakdown of the family structure	÷
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	Number of children	Number of families ^a
Parents	1-5	2077
One parent	1-8	1968
No parent	2-7	1779
	Total	5824

^aThe families with more than two generations are counted as separate families.

chosen at random from the total subjects of present study (18,604 members). They were genetically unrelated, because one person was chosen from each of 4500 random chosen families. The overlaps of blood relationship with three or more generation were avoided in these families. The allele and haplotype frequencies calculated from these 4500 people were very similar to the frequencies from the total subjects [allele frequencies (AF) data not shown].

Samples

DNA samples were obtained from peripheral lymphocytes or buccal cells using a JetQuick[®] Blood & Cell Culture Kits (GENOMED, Löhne, Germany) or QuickGene DNA Tissue Kit (KURABO, Osaka, Japan) according to the manufacturer's protocols.

HLA allele typing

HLA (-A, -C, -B, and -DRB1) four-digit allele typing was performed using Luminex 200 system (Luminex, Austin, TX) and WAKFlow HLA Typing kit (Wakunaga, Hiroshima, Japan) (10-12). HLA alleles were assigned automatically using WAKFLOW Typing software (Wakunaga, Hiroshima, Japan). The primer sequences of WAKFLOW Typing kit are specifically designed to make allele determination easier in Japanese population, and by default the analysis with WAKFLOW Typing software is based on the AF of the donors registered with Japan Marrow Donor Program (JMDP) which are available on the website, www.bmdc.jrc.or.jp (9). Therefore, this method can determine alleles with frequencies of 0.1% and greater in the Japanese population. A few alleles which could not be determined by this method as rare alleles were considered as secondary; these alleles were determined using Luminex 200 system and LAB Type SSO kit (One Lambda, Los Angeles, CA) assigned using the HLA Fusion software (One Lambda). In brief, exon 2 for HLA-DRB1; exons 2 and 3 for HLA-A, -B, and -C were amplified in these methods.

Haplotype determination

The haplotypes were determined by segregation. This study was designed with the aim to assess genetic linkage with high certainty. Nevertheless, the results also included some partial haplotypes because of the possibility of one or more recombination



Figure 1 Avoiding haplotype duplication. The extended haplotypes of a and c are redundant in families 1 and 2. In this case, six haplotypes were counted as family 1+2.

in a family. The haplotype frequencies were calculated by using haplotypes without taking into account the recombination. Thus, we counted the haplotypes of parents and not of children because fathers and mothers are genetically unrelated, while the haplotypes created by recombination were those of children only. Some haplotypes of parents whose children had recombinant haplotypes could not been determined because of two patterns of their combinations. These haplotypes were determined and counted as not less frequent but frequent haplotype phase. Specifically, assuming that four haplotypes are Hp1, Hp2, Hp3, and Hp4, those frequencies are HF1, HF2, HF3, and HF4, and two estimable phases are 'Hp1, Hp2' and 'Hp3, Hp4', HF1 was multiplied by HF2, HF3 was multiplied by HF4, and the haplotypes of the estimable phase with larger product were counted.

For the comparison to the result by MLE, the haplo.em program, which was evaluated by HAPLO.STATS (version 1.6.0) software operated in the R language, was used (13–16). For genetic markers measured on unrelated subjects with linkage phase unknown, this program computes the maximum likelihood estimates of haplotype probabilities using the progressive insertion algorithm that progressively inserts batches of loci into haplotypes of growing lengths.

Table 2	HLA-A,	-C, ·	-В,	-DRB1	allele	frec	luencies	in	Japan ^a
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A1 A*01.01 0.401 Cw1 C*01.02 17604 B7 B*07.02 5.830 DR1 DR1*01.01 6.823 A*02.01 11.820 Cw2 C*01.02 0.286 B*07.30 0.005 DR4 DR1*01.01 6.823 A*02.07 3.461 Cw4 C*04.02 0.026 B*07.31 0.005 DR4 DR1*0.406 13.481 A*02.28 0.000 Cw6 C*05.01 0.381 B*13 DR1 DR1*0.403 3.683 A*02.28 0.005 Cw7 C*07.02 1.27.14 B18 B*160.10 0.005 DR81*04.01 0.533 A*10.213 0.005 C*07.01 0.73 B*55.12 0.005 DR81*04.02 0.054 A*11.02 0.217 Cw80.2 1.361 B*27.05 0.063 DR81*04.02 0.056 A*11.02 0.216 Cw10 C*03.03 1.361 B*27.06 0.065 DR81*04.01 0.410 0.410 0.410 0.410 0.410	HLA-A serological specificity	HLA-A allele	GF (%)	HLA-C serological specificity	HLA-C allele	GF (%)	HLA-B serological specificity	HLA-B allele	GF (%)	HLA-DRB1 serological specificity	HLADRB1 allele	GF (%)
A A C C C C C D	Λ 1	Δ * O1 · O1	0.401	C) 4/1	C*01.02	17604	D7	P*07.02	5 620	DP1		E 022
A 402.06 9.083 Cw2 C 402.02 0.095 B 477.31 0.006 DR4 OHB 1 464.05 3.490 A 402.07 3.461 Cw4 C 402.02 0.005 B 470.31 0.006 DR8 1 404.05 3.305 A 402.26 0.010 Cw6 C 405.01 0.318 B 13.02 0.225 DR8 1 40.10 2.18 A 402.13 0.005 C 470.70 0.714 B 18 B 18.01 0.005 DR8 1 40.40 0.254 A 202.03 0.065 C 470.70 0.274 B 18 B 18.01 0.005 DR8 1 40.40 0.254 A 203.0 A.330.0 0.396 C 470.70 0.255 B 27.06 0.065 DR8 1 40.40 0.054 A 11.0 A.11.00 9.175 C 470.50 0.256 B 27.06 0.056 DR8 1 90.41 0.303 A 11.0 9.175 C 470.20 0.265 B 475.00 0.056 DR8 1 90.41 0.05 A 11.0 9.172 DR8 1 70.01 0.305 B 27.00	Δ2	A 01.01 A*02·01	11 620	CVVI	C*01.02	0.318	D7	B*07:02	0.026	DIT	DRB1*01.01	0.016
Ar0207 3.461 Dual C 1000 4.410 B6 B*0601 0.1078 Dubbit 104.06 3.305 A*02.18 0.078 Cubb C*05.01 0.308 B*13.01 1.173 DHB 1*04.01 3.954 A*02.05 0.005 CuV C*070.2 1.27.14 B18 B*16.01 0.005 DHB 1*04.01 0.574 A*02.03 0.063 C*070.0 0.375 B*27.05 0.836 DHB 1*04.01 0.574 A*03.01 0.396 C*06.01 3.351 B*27.05 0.035 DHB 1*04.02 0.055 A*11.04 0.396 C*06.02 1.355 B*27.05 0.035 DHB 1*04.02 0.056 A*11.04 0.015 Cw10 C*03.02 0.588 B*35.01 0.026 DHB 1*06.03 0.026 A*11.04 0.015 Cw102 C*11.02 1.1182 B*35.01 0.026 DHB 1*06.00	72	A*02.01	9.081	Cw/2	C*02.02	0.026		B*07:31	0.020	DR4	DRB1*04:05	13 491
Ar02:18 Ou78 Ou78 Core C 106:01 OL81 B 13:01 B 13:01 D 181 '14:03 OL83 Ar02:18 Ou00 Cv6 C 166:02 0.806 B 13:02 0.267 D RB 1'04:01 0.153 Ar02:13 0.005 C 170:04 0.282 B 22.0 B 76:03 0.005 D RB 1'04:07 0.573 Ar03:01 0.386 C 470:01 0.73 B *27:04 0.18 D RB 1'04:17 0.055 Ar10 A'10:0 9.17 C 406:02 0.026 B *27:06 0.065 D RB 1'04:11 0.05 Ar11.0 9.17 C 406:02 0.026 B *27:06 0.05 D RB 1'06:07 0.339 Ar11.05 0.039 C 40:02 C 40:02 B *35:05 0.066 D RB 1'06:07 0.329 Ar24.04 0.16 C 41:202 B *11 B *35:05 0.065 D RB 1'06:07 0.422 Ar24.05 0.021 C *12:02 11:182 B *36:01 0.045 D RB 1'110:05 0.0		A*02.00	3 461	Cw4	C*04·01	4 4 10	B8	B*08:01	0.016	BIII	DRB1*04:06	3 388
Ar0228 0.010 Cw68 Cr0702 12.74 B18 B*1302 0.267 DB81*04.01 2.184 Ar0213 0.005 Cw77 C70704 0.928 B22 B*6613 0.005 DB81*04.01 2.184 Ar0213 0.005 C*07074 0.928 B22 B*6612 0.005 DB81*04.01 2.184 Ar030 0.0396 C*07074 0.926 B*27.05 0.035 DB81*04.01 2.056 Ar0301 0.996 C*0601 3.351 B*27.05 0.035 DF81*14.45 0.005 Ar11101 0.911 Cw60 C*0330 13.053 B355 B*35.01 0.283 0.005 DF81*14.02 0.83 8.320 A*11102 0.015 Cw10 C*12.02 1.182 B*35.04 0.005 DF81*06.07 0.334 8.320 A*24.02 0.067 C*12.02 1.182 B*35.04 0.006 DF81*06.07 0.035 DF81*06.07 0.334 0.006 DF81*06.07 <t< td=""><td></td><td>A*02:18</td><td>0.078</td><td>Cw5</td><td>C*05:01</td><td>0.381</td><td>B13</td><td>B*13:01</td><td>1.173</td><td></td><td>DRB1*04:03</td><td>3.055</td></t<>		A*02:18	0.078	Cw5	C*05:01	0.381	B13	B*13:01	1.173		DRB1*04:03	3.055
A*0208 0.005 C.W7 C*07.02 2.714 B18 B*160 0.075 DBB1*04.01 0.573 A203 A*02.03 0.005 C*07.01 0.737 B*55.12 0.005 DBB1*04.02 0.255 A210 A*02.03 0.386 C*08.01 7.365 B27 B*27.05 0.663 DBB1*04.01 0.256 A710 A*10.05 0.094 C*08.02 0.266 B*27.05 0.663 DB60 DB81*04.01 0.339 A*11.05 0.219 CW10 C*03.02 0.668 B*35.05 0.056 DB60 DB81*06.01 0.242 A*24.02 0.021 C*14.02 0.831 B37 B*35.05 0.05 DB61*06.00 0.423 A*24.02 0.042 Cw14 C*14.02 6.871 B38 B*36.02 0.231 DB61*10.00 0.428 A*24.04 0.061 Cw15 C*15.03 0.051 B*38.00 0.201 DB61*10.00 0.428 A*24.03 0.002 Cw12 C*16.03 0.005 B*39.01 0.311 DB61*11.00 0		A*02:28	0.010	Cw6	C*06:02	0.808		B*13:02	0.287		DRB1*04:10	2.153
A*02:13 0.005 C*07.04 0.928 B22 B*16:00 0.075 DRB1*04.07 0.735 A/02:10 0.336 C*08.01 7.355 B27.0 9.103 DRB1*04.01 0.005 A/10:01 0.336 C*08.03 1.361 B27.08 0.085 DRB1*04.01 0.005 A/11 A*11.02 0.179 C*09 C*03.02 0.266 B*25.06 0.05 DRB1*04.01 0.383 8.320 A/11.05 0.005 C*03.02 0.281 B*35.06 0.016 DRB1*06.00 0.024 A/24.02 3.075 C/01.2 C*12.02 0.083 B37 B*35.00 DRB DRB1*06.00 0.024 A/24.03 0.012 C*12.02 0.081 B39 B*39.00 DRB DRB1*0.00 0.438 A*24.04 0.001 C*16.02 3.081 B39 B*39.00 DRB DRB1*10.01 0.438 A*24.04 0.005 C*17.02 3.081 B39 B*39.00 DRB DRB1*10.01 0.438 A*24.04 0.005 C*17.05 0		A*02:05	0.005	Cw7	C*07:02	12.714	B18	B*18:01	0.005		DRB1*04:01	0.954
A202 A102.00 0.063 C*07.01 0.073 B*5.12 0.081 D*11*0.40 0.252 A210 A103.01 0.396 C*08.01 7355 B27.04 0.185 D*11*1.04 0.005 A11 A11.01 9.17 C*09.02 0.026 B*37.06 0.061 D*60 D*11*1.44 0.005 A11.0 0.171 C*09 C*03.02 0.568 B*35.06 0.056 D*81 D*81*0.02 2.42 A24.02 0.042 C*04.02 C*12.02 11.82 B*35.05 0.016 D*81*10.60 1.4.233 A24.4 A*24.02 0.042 C*12.02 0.038 B37 B*35.05 0.016 D*81*10.60 1.4.233 A24.04 0.042 C.041 C*14.02 0.81 B38 B*38.00 0.016 D*11 D*81*11.01 2.518 A*24.04 0.016 C.0412 C*15.02 0.016 B391 B*392.00 0.021 D*81*11.01 0.101 D*81*11.01 0.101 D*81*11.01 0.101 D*81*11.01 0.101 D*81*11.01 0.101 <td></td> <td>A*02:13</td> <td>0.005</td> <td></td> <td>C*07:04</td> <td>0.928</td> <td>B22</td> <td>B*56:03</td> <td>0.177</td> <td></td> <td>DRB1*04:07</td> <td>0.573</td>		A*02:13	0.005		C*07:04	0.928	B22	B*56:03	0.177		DRB1*04:07	0.573
A?02.00 0.386 Cw8 C*08.01 3361 B*27.04 0.88 DRB1*04.02 0.005 A3 A*03.02 0.094 C*08.02 0.026 B*27.06 0.035 DRB DRB1*04.02 0.005 A11 A*11.02 0.219 Cw10 C*03.03 13.053 B35 B*35.04 0.005 DRB DRB1*07.01 0.339 A11 A*11.02 0.219 Cw10 C*03.02 12.831 B*35.04 0.005 DRB1*06.02 4.207 A24 A*24.02 0.675 Cw12 C*12.03 0.083 B37 B*35.04 0.005 DRB1*06.00 4.292 A24.04 0.070 C*12.03 0.688 B38 B*36.01 0.016 DRB1*10.01 4.41 A*24.07 0.021 C*116.02 3.081 B39 B*38.02 0.281 DRB1*11.01 0.101 A*24.04 0.016 C*15.02 3.061 B*39.01 0.016 DR1*111.00 0.017 A*24.05 0.005 Cw17 C*15.10 0.005 B*39.02 0.036 DR1	A203	A*02:03	0.063		C*07:01	0.073		B*55:12	0.005		DRB1*04:04	0.255
A3A*03.010.396C*08.020.106D*27.050.005D*11*040.005A111A*11.020.219C*00.020.268B*35.018.263DR1DR1*07.010.339A*11.020.219C×01.01C*03.0412.391B*35.050.006DR8DR1*06.038.320A24A*24.0236.475C×01.2C*12.0211.162B*35.050.005DR1*06.030.042A24.0236.475C×01.2C*12.0211.162B*35.050.016DR1*06.000.424A*24.020.021C×11.030.083B*33.020.281DR100.434A*24.040.021C*11.023.083B*38.020.281DR100.44A*24.050.006C*15.050.016B*38.020.016DR11*1.012.181A*24.040.021C*11.050.006B*39.013.231DR1*11.010.005A*24.050.006C*15.100.006B*39.013.231DR1*11.023.74A24.03A*24.030.005C×07.150.010B3901B*39.010.331DR1*11.021.814A24.040.005C×07.150.010B440B*41.020.361DR1*11.025.068A*26.050.068C*03.430.010B441B*41.020.375DR1*11.4543.244A26.050.010C*01.510.056B451B*41.020.365DR1*11.4613.244A26.050.021C*0	A210	A*02:10	0.386	Cw8	C*08:01	7.355	B27	B*27:04	0.188		DRB1*04:02	0.005
A*03.02 0.094 C*03.02 0.056 B*27.06 0.056 DR6 DR81*14.46 0.005 A111 0.101 9.117 C:v30 C*03.02 12.891 B*35.04 0.005 DR81*08:00 8.233 A24 A*24.02 36.75 C:v12 C*13.02 1.825 B*35.04 0.005 DR81*08:00 4.207 A24 A*24.02 0.705 C.v12 C*12.03 0.038 B37 B*35.04 0.005 DR81*08:00 4.203 A*24.04 0.004 C.v14 C*14.03 6.688 B*38.01 0.016 DR11 DR1*11.00 1.4283 A*24.07 0.021 C.v14 C*16.02 3.081 B39 B*38.01 0.016 DR11*11.01 0.105 A*24.04 0.005 C.v17 C*15.02 3.081 B39 B*39.01 0.015 DR1*1*1.016 0.05 A*24.03 0.005 C.v17 C*15.10 0.006 B*39.02 0.305 DR1*1 DR1*1.101 0.105 A*24.03 0.005 C.v17 C*15.10 0.010 B*	A3	A*03:01	0.396		C*08:03	1.361		B*27:05	0.063		DRB1*04:11	0.005
A11 A+11.01 9.117 Cw9 C*03.03 13.053 B35 B*35.05 0.06 DR8 DR81*06.00 8.320 A24 A*24.02 0.065 C*03.02 0.568 B*35.05 0.005 DR81*06.00 4.207 A24 A*24.02 0.647 C*12.02 11.122 B*35.04 0.005 DR81*06.00 4.207 A*24.08 0.042 C*14.02 6.871 B38 B*36.04 0.005 DR81*0100 14.283 A*24.07 0.016 C*14.02 6.871 B39 B*39.04 0.005 DR81*11.00 0.016 A*24.07 0.016 Cw15 C*15.02 3.081 B39 B*39.04 0.005 DR81*11.00 3.74 A*24.05 0.005 C*15.05 0.016 B*39.02 0.035 DR81*11.00 3.74 A*24.05 0.005 C*07.17 C*17.00 0.010 B*39.02 0.005 DR81*12.02 5.44 A*26.02 1809 C*03.43 0.000 B*199.02 0.005 DR81*14.02 0.005 DR81*14.02 0.005		A*03:02	0.094		C*08:02	0.026		B*27:06	0.005	DR6	DRB1*14:45	0.005
A*11.02 0.219 Cw10 C*03.04 12.391 P136.05 0.016 DRB DRB1*08:02 4.207 A24 A*24.02 0.6475 Cw12 C*12.02 11.182 P135.35 0.005 DRB1*08:02 4.207 A24 0.709 C*12.02 11.182 P135.35 0.005 DRB DRB1*08:01 0.428 A*24.02 0.014 C*14.02 6.871 B38 B*38.02 0.281 DR1 DRB1*10:00 0.44 A*24.04 0.016 C*15.02 3.081 B39 B*39.04 0.029 DRB1*11:08 0.005 A*24.05 0.005 Cw15 0.016 P39.05 0.005 DRB1*12:02 1.814 A24.03 0.005 Cw17 C*17.10 0.010 B3901 B*39.01 3.031 DRB1*12:02 1.814 A24.03 0.005 Cw163 0.016 B*39.02 1.939 0.331 DRB1*12:02 1.814 A26.03 2.288 undefined C*03.43 0.010 B*44.02 0.375 DRB1*14.02 0.814 0.8144.54	A11	A*11:01	9.117	Cw9	C*03:03	13.053	B35	B*35:01	8.263	DR7	DRB1*07:01	0.339
A*11.05 0.006 C*03.02 0.568 B*35.03 0.005 DRB1*08.02 4.024 A24 A*24.02 36.475 Cw12 C*12.02 11.182 B*35.03 0.005 DRB1*08.01 14.283 A*24.02 0.709 C*12.02 10.83 B*37.01 0.49 DR9 DRB1*08.01 14.283 A*24.02 0.704 C*14.02 6.871 B*38.01 0.016 DR1 DRB1*11.00 2.518 A*24.07 0.016 Cw15 C*15.05 0.016 B*39.04 0.005 DR11 DR1*11.00 3.74 A24.05 0.005 C*15.10 0.016 B*39.04 0.321 DRB1*11.00 3.74 A24.03 A*24.03 0.005 Cw17 C*17.10 0.010 B*39.01 3.221 DRB1*13.00 DS5 A26.03 2.288 C*03.43 0.010 B41 B*41.02 0.057 DR1*1 DR1*13.01 DS6 A*26.02 1.669 C*03.40 0.005 B*44.02 3.75 DR14 DR1*14.02 0.75 A*26.02 1		A*11:02	0.219	Cw10	C*03:04	12.391		B*35:05	0.016	DR8	DRB1*08:03	8.320
A24 A*2402 36.475 Cw12 C*12.02 11.82 B*36.00 0.05 DRB1*08:00 0.428 A*24.02 0.709 Cw14 C*12.02 0.831 B33 B*36.00 0.281 DR10 DRB1*00:01 1.4.283 A*24.07 0.01 Cw14 C*14.02 6.861 B*38.00 0.06 DR11 DRB1*11.00 0.044 A*24.04 0.06 Cw15 C*15.02 3.081 B39 B*39.00 0.06 DRB1*11.08 0.05 A*24.05 0.005 Cw17 C*11.01 0.005 B*39.02 0.005 DR121 DRB1*11.02 3.74 A2403 A*26.07 0.005 Cw17 C*11.01 0.005 B*39.02 0.305 DR13 DRB1*1.02 3.74 A2403 A*26.07 7.30 undefined C*03.23 0.00 B*39.02 0.305 DR13 DRB1*1.02 3.74 A260 1.069 Cw17 C*11.50 0.005 B44 B*40.00 0.005 DRB1*14.01 3.20 A27 0.060 0.000 C		A*11:05	0.005		C*03:02	0.568		B*35:04	0.005		DRB1*08:02	4.207
A*24.20 0.709 C*12.03 0.83 B37 B*38.00 0.45 DR9 DR91 00.01 14.24 A*24.07 0.021 C*14.02 6.871 B38.00 0.201 DR91*11.00 0.161 DR91*11.00 0.161 A*24.07 0.016 Cw15 C*15.02 3.081 B39 B*39.00 0.05 DR91 DR91*11.00 0.06 A*24.05 0.006 Cw15 C*15.02 3.081 B39 B*39.00 3.021 DR91*11.00 0.016 0.016 DR11 0.016 0.016 0.011 DR91*11.00 0.161 0.005 DR14 0.010 DR14 0.010 DR14 DR11.00 0.01 DR14 DR11.00 DR14 DR14.10 D.00 DR14	A24	A*24:02	36.475	Cw12	C*12:02	11.182		B*35:35	0.005		DRB1*08:09	0.042
A*24.00 0.042 Cw14 C*14.02 6.871 B38 B*38.02 0.281 DR10 DR110 DR111.00 0.251 A*24.07 0.016 Cw15 C*15.02 3.061 B39 B*39.04 0.029 DR1111.00 0.016 A*24.25 0.005 C*15.05 0.016 B*39.05 0.035 DR12 DR1*11.00 0.017 A2403 A*24.07 0.005 Cw17 C*17.01 0.010 B3901 B*39.00 3.21 DR1*11.00 0.43 A2403 A*26.01 7.360 undefined C*03.23 0.010 B4301 B*39.01 3.21 DR1*13.07 0.05 A*26.02 1.809 C*07.15 0.010 B44 B*41.02 0.67 DR1*13.07 0.05 A*26.03 0.068 C*07.15 0.010 B44 B*41.02 0.75 DR1*11.405 2.090 A*26.04 0.068 C*07.15 0.010 B44 B*41.02 0.75 DR1*11.405 2.090 A*29.01 0.010 C*16.04 0.05 B45 B*45.01		A*24:20	0.709		C*12:03	0.083	B37	B*37:01	0.495	DR9	DRB1*09:01	14.283
A*24.070.021C*14.036.688B*39.010.016DR1DR1*11.080.016A*24.040.016Cw15C*15.023.081B39B*39.020.031DRB*11.080.005A*24.050.005C*15.100.005B*39.020.301DRB*12.013.74A2400A*24.030.005Cw17C*17.010.010B3902B*39.020.308DR13DRB*13.025.948A*26.021.099C*03.230.010B41B*44.020.055DRB*13.070.589A*26.021.099C*03.640.005B44B*44.020.751DRB*13.070.589A*26.020.068C*03.430.005B44B*44.020.751DRB*14.543.274A*26.020.068C*03.440.005B44B*44.020.751DRB*14.543.274A*26.020.068C*03.440.005B45B*45.014.765DRB*14.543.274A29A*26.050.068C*03.450.005B46B*46.014.765DRB*14.543.274A30A*30.010.209C*04.150.005B46B*46.014.765DRB*14.543.274A31A*30.010.21C*04.150.005B46B*46.014.765DRB*14.1200.675A31A*31.010.012C*04.15B510B.7510.235DR14.03DRB*14.1200.676A32A*32.010.012C*16.14B510B.751 <td></td> <td>A*24:08</td> <td>0.042</td> <td>Cw14</td> <td>C*14:02</td> <td>6.871</td> <td>B38</td> <td>B*38:02</td> <td>0.281</td> <td>DR10</td> <td>DRB1*10:01</td> <td>0.474</td>		A*24:08	0.042	Cw14	C*14:02	6.871	B38	B*38:02	0.281	DR10	DRB1*10:01	0.474
A*24.04 0.016 Cw15 C*15.02 3.081 B39 B*39.04 0.209 DRB**11.06 0.016 A*24.25 0.005 C*15.00 0.005 B*39.02 0.203 DRB**12.01 3.774 A2403 A*24.05 0.005 Cw17 C*17.01 0.010 B3901 3.221 DRB**13.02 5.484 A2403 A*26.03 2.288 C*03.43 0.010 B41 B*41.02 0.005 DRB**13.01 0.589 A*26.05 0.688 C*03.43 0.010 B44 B*41.02 0.055 DRB**13.01 0.059 A*26.05 0.668 C*03.43 0.005 B44 B*41.02 0.075 DRB**14.04 1.303 A*26.05 0.668 C*04.15 0.005 B46 B*46.01 0.65 DRB**14.07 0.109 A29 A*29.01 0.010 C*16.04 0.005 B46 B*46.01 0.65 DRB**14.02 0.65 A311 A*30.01 0.201 C*16.04 0.005 B46 B*45.01 0.005 DRB**14.02 0.65		A*24:07	0.021		C*14:03	6.688		B*38:01	0.016	DR11	DRB1*11:01	2.518
A*24:05 0.010 C*15:05 0.016 B*39:23 0.031 DRB1*11:08 0.005 A24:05 0.005 Cw17 C*17:01 0.010 B3901 B*39:02 0.305 DR12 DRB1*12:02 3.744 A263 A*26:01 7.350 undefined C*03:23 0.010 B3902 B*39:02 0.308 DR13 DRB1*13:02 5.484 A26:03 2.288 C*03:43 0.010 B41 B*41:02 0.305 DR14 DRB1*13:07 0.005 A*26:05 0.068 C*07:15 0.010 B44 B*44:02 0.375 DR1*14:06 1.303 A29 A*26:06 0.001 C*04:15 0.005 B45 B*46:01 4.765 DR81*14:02 0.005 A30 A*30:01 0.201 C*16:04 0.005 B46 B*46:01 4.765 DR81*14:02 0.067 A33 A*30:01 0.021 F*16:04 0.005 B*16:0 0.875 DR81*14:02 0.067 A33 A*30:01 0.021 F*16:04 0.005 B*16:02 0.875		A*24:04	0.016	Cw15	C*15:02	3.081	B39	B*39:04	0.209		DRB1*11:06	0.016
A*24.03 0.005 Cw17 C*15:10 0.005 B*39:05 0.005 DR1*12:02 1.814 A260 A*26:01 7.350 undefined C*03:23 0.010 B3902 B*39:02 0.308 DR13 DRB1*13:02 5.948 A260 A*26:03 2.288 C*03:43 0.010 B41 B*41:02 0.005 DRB1*13:00 0.000 A*26:05 0.068 C*03:64 0.005 B44:02 0.375 DR14 DRB1*14:54 3.274 A*26:05 0.068 C*03:64 0.005 B45 B*46:01 0.005 DRB1*14:06 1.303 A420:01 0.010 C*04:15 0.005 B46 B*46:01 4.765 DRB1*14:02 0.057 A30 A*30:01 0.209 E*16:02 0.865 B*46:01 0.765 DRB1*14:02 0.057 A31 A*31:01 8.403 S DR1*14:02 0.57 DR1*14:02 0.57 A33 A*32:01 0.010 D B51 B*51:01 8.925 DR1404 DRB1*14:04 0.005		A*24:25	0.010		C*15:05	0.016		B*39:23	0.031		DRB1*11:08	0.005
A2403 A*26:01 7.360 CM17 C*17.01 0.010 B3901 B*39.01 3.21 DRB1*12.02 1.814 A26 A*26:01 7.350 undefined C*03:32 0.010 B43002 B*39:02 0.308 DR13 DRB1*13:02 5.948 A*26:02 1.809 C*07:15 0.010 B44 B*44:02 0.375 DR14 DRB1*13:07 0.005 A*26:05 0.068 C*07:15 0.010 B44 B*44:02 0.375 DR14 DRB1*14:05 2.090 A226:06 0.010 C*16:04 0.005 B46 B*4:01 4.765 DRB1*14:05 2.090 A30 A*30:01 0.029 C*16:04 0.005 B46 B*4:01 2.878 DRB1*14:02 0.057 A31 A*31:01 8.403 2.871 DRB1*14:02 0.057 DRB1*14:02 0.056 A32 A*30:01 0.010 C*16:04 0.005 B48 B*46:01 2.878 DRB1*14:02 0.056 A33 A*31:01 0.501 DRB1*16:01 0.52 DRB1*		A*24:05	0.005		C*15:10	0.005		B*39:05	0.005	DR12	DRB1*12:01	3.774
A26 A*26:01 7.350 undefined C*03:23 0.010 B3902 B*39.02 0.308 DR13 DRB1*13:01 0.589 A*26:02 1.809 C*07:15 0.010 B44 B*44:02 0.375 DR14 DRB1*13:01 0.005 A*26:06 0.008 C*03:64 0.005 B45 B*46:01 0.005 DRB1*14:05 2.090 A26:06 0.010 C*04:15 0.005 B46 B*46:01 0.005 DRB1*14:06 1.303 A30 A*30:01 0.209 - B48 B*46:02 0.005 DRB1*14:02 0.057 A*30:01 0.001 C*04:15 0.005 B46 B*46:01 2.878 DRB1*14:02 0.057 A31 A*30:01 0.021 - B510 B*5100 0.016 DRB1*14:12 0.026 A32 A*32:01 0.021 - B5102 B*5102 0.055 DR1400 DRB1*14:02 0.056 A33:01 0.010 - B5102 B*5102 0.055 DR141 0.016 DRB1*16:01 7.7	A2403	A*24:03	0.005	Cw17	C*17:01	0.010	B3901	B*39:01	3.321		DRB1*12:02	1.814
A*26:03 2.288 C*03:33 0.010 B41 B*41:02 0.005 DRB1*13:01 0.589 A*26:05 0.068 C*07:15 0.010 B44 B*44:03 6.751 DR14 DRB1*13:01 0.058 A*26:06 0.010 C*03:64 0.005 B45 B*46:01 0.005 DRB1*14:05 2.090 A*26:06 0.010 C*16:04 0.005 B46 B*46:01 4.765 DRB1*14:07 0.103 A30 A*30:01 0.209 B46 B*46:01 4.765 DRB1*14:02 0.057 A*30:04 0.021 B48 B*48:01 2.878 DRB1*14:02 0.057 A31 A*31:01 8.403 5501 B5102 B*51:01 8.925 DRB1*14:02 0.066 A*33:01 0.001 - B5102 B*51:03 0.005 DR14:04 DRB1*15:01 7.778 A*40:01 0.005 B53 B*51:03 0.005 DR14:04 DRB1*15:01 0.776 A*46:0 0.000 B52 B52:01 1.030 DR15 DRB1*15:02 </td <td>A26</td> <td>A*26:01</td> <td>7.350</td> <td>undefined</td> <td>C*03:23</td> <td>0.010</td> <td>B3902</td> <td>B*39:02</td> <td>0.308</td> <td>DR13</td> <td>DRB1*13:02</td> <td>5.948</td>	A26	A*26:01	7.350	undefined	C*03:23	0.010	B3902	B*39:02	0.308	DR13	DRB1*13:02	5.948
A*26:02 1.809 C*07:15 0.101 B44 B*44:02 6.751 DRB*13:07 0.005 A*26:06 0.000 C*04:15 0.005 B*45:01 0.005 DR14 DRB*14:06 3.274 A29 A*29:01 0.010 C*16:04 0.005 B46 B*46:01 0.05 DRB*14:06 1.303 A30 A*30:04 0.029 B48 B*46:01 0.016 DRB*14:02 0.05 A31 A*31:01 8.403 0.021 B48 B*46:01 0.016 DRB*14:12 0.026 A33 A*33:01 0.001 C*16:04 D.005 B5102 B*51:01 8.925 DRB*14:129 0.016 A33 A*33:01 0.010 B5102 B*51:02 0.055 DR140 DRB*14:129 0.106 A*34:01 0.010 B5103 B*51:03 0.055 DR140 DRB*14:102 1.650 A68 A*66:01 0.005 B5102 B*51:03 0.005 DR140 DRB*15:04 0.005 Null A*03:01 0.010 B56		A*26:03	2.288		C*03:43	0.010	B41	B*41:02	0.005		DRB1*13:01	0.589
A*26:05 0.068 C*03:64 0.005 B*44:02 0.375 DR14 DRB1*14:54 3.274 A*26:06 0.010 C*04:15 0.005 B45 B*46:01 4.765 DRB1*14:05 2.090 A30 A*30:01 0.209 B*46:02 0.005 DRB1*14:02 0.057 A*31:01 8.403 0.021 B48 B*46:01 2.780 DRB1*14:02 0.057 A31 A*31:01 8.403 B50 B*50:01 0.016 DRB1*14:02 0.057 A33 A*33:03 7.507 B5102 B51:02 0.235 DR140 DRB1*14:03 1.569 A*33:01 0.010 B5103 B*51:02 0.235 DR14 DRB1*15:02 10.650 A*6:01 0.005 B53 B*51:02 0.05 DR14 DRB1*15:02 10.690 Null A*02:53N 0.010 B53 B*52:01 10.93 DR16 DRB1*15:02 10.690 Null A*26:18 0.005 B56 B*50:01 0.05 DR14 DRB1*06:02 0.97		A*26:02	1.809		C*07:15	0.010	B44	B*44:03	6.751		DRB1*13:07	0.005
A*26:06 0.010 C*04:15 0.005 B46 B*46:01 4.765 DRB1*14:05 2.090 A29 A*30:01 0.209 B*46:02 0.005 DRB1*14:02 0.057 A30 A*30:04 0.021 B48 B*48:01 2.878 DRB1*14:02 0.057 A31 A*31:01 8.403 B50 B*50:01 0.016 DRB1*14:02 0.057 A33 A*33:01 0.021 B51 B*51:02 0.235 DR1403 DRB1*14:02 0.067 A33 A*33:01 0.010 B5102 B*51:02 0.235 DR1404 DRB1*14:03 1.569 A*33:01 0.010 B5103 B*51:03 0.005 DR1404 DRB1*14:02 0.057 A68 A*68:01 0.010 B53 B5502 2.48 DR16 DRB1*15:02 0.059 Null A*02:53N 0.010 B56 B561 0.305 DR14 DRB1*04:57 0.005 A*11:43 0.005 B56 B561 0.589 Undefined DR1*04:57 0.005		A*26:05	0.068		C*03:64	0.005		B*44:02	0.375	DR14	DRB1*14:54	3.274
A29 A729:01 0.010 C*16:04 0.005 B46 B*46:01 4.765 DRB1*14:06 1.303 A30 A*30:04 0.209 B*46:02 0.005 DRB1*14:02 0.057 A31 A*31:01 8.403 B50 B*46:01 2.878 DRB1*14:12 0.026 A32 A*32:01 0.021 B51 B*51:01 8.925 DRB1*14:04 0.010 A33 A*33:03 7.507 B5102 B*51:02 0.235 DR14:04 DRB1*14:04 0.010 A34 A*34:01 0.010 B5103 B*51:01 8.925 DRB1*1:502 10.650 A*33:01 0.010 B5103 B*51:02 0.055 DR81*1:502 10.650 A66 A*66:01 0.005 B53 B*53:01 0.005 DR81*1:502 10.650 Null A*02:53N 0.010 B55 B55:02 2.648 DR16 DR81*1:602 0.897 Null A*20:48 0.005 B56 B*55:01 0.005 DR81*06:27 0.005 A*24:88 0.005	100	A*26:06	0.010		C*04:15	0.005	B45	B*45:01	0.005		DRB1*14:05	2.090
A30 A'30:01 0.209 B48:02 0.005 DRB1*14:07 0.109 A31 A'30:04 0.021 B48 B*48:01 2.878 DRB1*14:02 0.057 A32 A'32:01 0.021 B51 B*51:01 8.925 DRB1*14:03 1.569 A33 A'33:03 7507 B5102 B*51:02 0.235 DR1404 DRB1*14:03 1.569 A'33:01 0.010 B5103 B*51:02 0.005 DR1*14:103 1.569 A'33:01 0.010 B5103 B*51:02 0.005 DRB1*14:04 0.010 A66 A*66:01 0.005 B5103 B*51:01 0.005 DRB1*15:04 0.005 Null A*02:53N 0.010 B54 B*54:01 7.491 DRB1*16:02 0.897 Undefined A*24:46 0.010 B56 B*55:02 2.648 DR16 DRB1*0:20 0.055 A*24:48 0.005 B57 B*57:01 0.005 DR18*16:02 0.897 A*11:43 0.005 B57 B*59:01 0.043 DR1*0*15:	A29	A*29:01	0.010		C*16:04	0.005	B46	B*46:01	4.765		DRB1*14:06	1.303
A*3004 0.021 B48 B*48:01 2.878 DRB1*14:02 0.057 A31 A*31:01 8.403 B50 B*50:01 0.016 DRB1*14:02 0.026 A32 A*32:01 0.021 B51 B*51:01 8.925 DRB1*14:03 1.569 A33 A*33:01 0.010 B5102 B*51:02 0.025 DR1404 DRB1*14:04 0.010 A34 A*34:01 0.010 B53 B*51:01 0.005 DRB1*15:02 10.650 A66 A*66:01 0.005 B53 B*51:01 0.005 DRB1*15:02 10.650 Null A*02:53N 0.010 B54 B*51:01 7.491 DRB1*16:02 0.897 Undefined A*24:46 0.010 B56 B*56:01 0.483 DR16 DRB1*16:02 0.897 Undefined A*24:46 0.010 B56 B*56:01 0.483 DR16 DRB1*16:02 0.897 Undefined A*24:48 0.005 B57 B*57:01 0.005 DRB1*06:27 0.005 A*31:11 0.005 B59 B*59:01 0.433 DR1*08:23 0.005 B40 B40:02 7.945 B*40:02 7.945 <	A30	A*30:01	0.209				D 40	B*46:02	0.005		DRB1*14:07	0.109
A31 A*31:01 3.403 B50 B*50:01 0.016 DRB1*14:12 0.020 A32 A*32:01 0.021 B51 B*51:01 8.25 DR1403 DRB1*14:03 1.569 A33 A*33:03 7507 B5102 B*51:02 0.235 DR1403 DRB1*14:04 0.010 A34 A*34:01 0.010 B52 B*52:01 11.093 DR15 DRB1*15:02 10.650 A66 A*66:01 0.005 B53 B*53:01 0.005 DRB1*15:01 7.778 A68 A*66:01 0.010 B54 B*54:01 7.491 DRB1*15:04 0.005 Null A*02:53N 0.010 B55 B*55:02 2.648 DR16 DRB1*03:01 0.146 A*11:43 0.005 B56 B*56:01 0.850 undefined DRB1*03:05 0.005 A*24:88 0.005 B57 B*57:01 0.005 DR1 DRB1*08:23 0.005 A*31:11 0.005 B58 B*58:01 0.579 DR1*08:23 0.005 A*31:11 <t< td=""><td>A 0 1</td><td>A*30:04</td><td>0.021</td><td></td><td></td><td></td><td>B48</td><td>B^48:01</td><td>2.878</td><td></td><td>DRB1*14:02</td><td>0.057</td></t<>	A 0 1	A*30:04	0.021				B48	B^48:01	2.878		DRB1*14:02	0.057
A32 A*32.01 0.021 B51 B*51.01 8.925 DRB1*14:29 0.016 A33 A*33:03 7.507 B5102 B*51:02 0.235 DR1403 DRB1*14:04 0.010 A34 A*34:01 0.010 B5103 B*51:03 0.005 DR1404 DRB1*15:02 10.650 A66 A*66:01 0.005 B53 B*51:01 7.778 DRB1*15:01 7.778 A68 A*68:01 0.010 B54 B*54:01 7.491 DRB1*15:04 0.005 Null A*02:53N 0.010 B56 B*56:02 2.648 DR16 DRB1*16:02 0.897 Nuld A*20:446 0.010 B56 B*56:01 0.850 undefined DRB1*03:01 0.146 A*24:88 0.005 B56 B*56:01 0.850 undefined DRB1*03:23 0.005 A*26:18 0.005 B59 B*59:01 2.043 B*40:02 7.945 A*31:11 0.005 B61 B*40:02 7.945 B*40:66 4.791 B*40:60 8:40:03	AJI	A*31:01	8.403				B50	B " 50:01	0.016		DRB1*14:12	0.026
A33 A*33:03 7.507 B5102 B5102 0.235 DR1403 DRB1*14:03 0.010 A34 A*33:01 0.010 B5103 B*51:03 0.005 DR1404 DRB1*14:04 0.010 A66 A*66:01 0.005 B53 B*53:01 0.005 DR11*15:01 7.778 A68 A*68:01 0.010 B54 B*51:02 2.648 DR16 DRB1*16:02 0.897 Null A*02:53N 0.010 B55 B*55:02 2.648 DR16 DRB1*16:02 0.897 Undefined A*24:46 0.010 B56 B*56:01 0.850 undefined DR1*04:57 0.005 A*11:43 0.005 B56 B*56:01 0.850 undefined DR1*04:57 0.005 A*24:88 0.005 B57 B*57:01 0.005 DR81*08:23 0.005 A*31:11 0.005 B59 B*59:01 2.043 B*108:23 0.005 A*31:11 0.005 B60 B*40:01 5.348 B*40:50 0.016 B*40:50 0.016	AJZ	A^32:01	0.021				B51	B^51:01	8.925	DD1400	DRB1*14:29	0.016
A34 A*34:01 0.010 B503 B 51.03 0.003 DR1404 DR111:044 0.010 A66 A*66:01 0.005 B53 B*53:01 10.005 DRB1*15:01 7.778 A68 A*68:01 0.010 B54 B*54:01 7.491 DRB1*16:02 0.897 Null A*02:53N 0.010 B55 B*55:02 2.648 DR16 DRB1*16:02 0.897 Undefined A*24:46 0.010 B56 B*56:01 0.850 undefined DR1*03:01 0.146 A*11:43 0.005 B56 B*56:01 0.850 undefined DR1*04:57 0.005 A*24:88 0.005 B56 B*5610 0.850 undefined DR1*04:57 0.005 A*24:88 0.005 B57 B*5701 0.005 DR1*08:23 0.005 A*31:11 0.005 B59 B*59:01 5.748 0.005 DR1*08:23 0.005 B60 B*40:07 0.010 B*40:02 7.945 B*40:01 5.348 B*40:03 0.407 B*40:02 </td <td>A33</td> <td>A *22.03</td> <td>7.507</td> <td></td> <td></td> <td></td> <td>D0102 P5102</td> <td>D*51.02</td> <td>0.235</td> <td>DR 1403</td> <td>DRD1 14.03</td> <td>0.010</td>	A33	A *22.03	7.507				D0102 P5102	D*51.02	0.235	DR 1403	DRD1 14.03	0.010
A34 A 34.01 0.010 B52 B 52.01 10.053 DRB 115.02 10.050 A66 A *66:01 0.005 B53 B *53:01 0.005 DRB 1*15:01 7.778 A68 A *68:01 0.010 B54 B *54:01 7.491 DRB 1*15:04 0.005 Null A*22:53N 0.010 B55 B *56:02 2.648 DR16 DRB 1*16:02 0.897 Undefined A*24:46 0.010 B56 B *56:01 0.850 undefined DRB 1*03:01 0.146 A*11:43 0.005 B56 B *56:01 0.850 undefined DRB 1*04:57 0.005 A*26:18 0.005 B58 B *58:01 0.579 DRB 1*08:23 0.005 A*31:11 0.005 B59 B *59:01 2.043 B*40:02 7.945 B*40:02 7.0010 B*40:02 7.945 B*40:02 7.945 B*40:02 0.005 B*40:03 0.407 B*40:05 0.016 B*40:05 0.016 B*40:05 0.005 B*40:11 0.005 <td>A 2 4</td> <td>A*33.01</td> <td>0.010</td> <td></td> <td></td> <td></td> <td>D0103</td> <td>D*51.03</td> <td>0.005</td> <td></td> <td>DDD1 14.04</td> <td>10.010</td>	A 2 4	A*33.01	0.010				D0103	D*51.03	0.005		DDD1 14.04	10.010
A68 A*68:01 0.003 B53 B*53:01 0.003 DRB1*15:04 0.005 Null A*02:53N 0.010 B54 B*55:02 2.648 DR16 DRB1*15:04 0.005 Undefined A*24:46 0.010 B56 B*55:02 2.648 DR17 DRB1*10:01 0.146 A*11:43 0.005 B56 B*56:01 0.850 undefined DRB1*03:01 0.146 A*24:88 0.005 B56 B*56:01 0.850 undefined DRB1*03:01 0.146 A*24:88 0.005 B56 B*56:01 0.850 undefined DRB1*08:23 0.005 A*26:18 0.005 B58 B*59:01 2.043 DRB1*08:23 0.005 A*31:11 0.005 B60 B*40:01 5.348 B*40:52 0.005 B61 B*40:62 7.945 B*40:52 0.005 B61 B*40:02 7.945 B*40:50 0.016 B*40:53 0.005 B*40:50 0.016 B*40:50 0.016 B*40:50 0.016 B*40:53 0.005 B	A34 A66	A*34.01	0.010				D0Z D52	D*52.01	0.005	DRIS	DDD1*15.02	10.050
Null A*02:53N 0.010 B54 B 34.01 1.401 DHBT 16:02 0.897 Undefined A*24:46 0.010 B55 B55.02 2.648 DR16 DRB1*00:2 0.897 A*11:43 0.005 B56 B*56:01 0.850 undefined DR17 DRB1*03:01 0.146 A*24:88 0.005 B56 B56:01 0.850 undefined DRB1*04:57 0.005 A*26:18 0.005 B57 B*57:01 0.005 DRB1*08:23 0.005 A*31:11 0.005 B59 B*59:01 2.043 B60 B*40:01 5.348 B60 B*40:07 0.010 B*40:52 0.005 B61 B*40:02 7.945 B*40:52 0.005 B61 B*40:02 7.945 F <td>A68</td> <td>A 68.01</td> <td>0.005</td> <td></td> <td></td> <td></td> <td>B54</td> <td>B*5/-01</td> <td>7/91</td> <td></td> <td>DRB1*15:0/</td> <td>0.005</td>	A68	A 68.01	0.005				B54	B*5/-01	7/91		DRB1*15:0/	0.005
Undefined A*24:46 0.010 B*55:04 0.130 DR17 DRB1*03:01 0.146 A*11:43 0.005 B56 B*56:01 0.850 undefined DRB1*04:57 0.005 A*24:88 0.005 B57 B*57:01 0.005 DRB1*08:23 0.005 A*26:18 0.005 B58 B*58:01 0.579 DRB1*08:23 0.005 A*31:11 0.005 B59 B*59:01 2.043 E*40:67 0.010 B*40:52 0.005 B61 B*40:02 7.945 E*40:66 4.791 B*40:50 0.016 B*40:53 0.005 B*40:50 0.016 E*40:53 0.005	Null	A *02.53N	0.010				B55	B*55.02	2.6/18	DB16	DRB1*16:02	0.000
A*11:43 0.005 B56 B*56:01 0.850 undefined DRB1*04:57 0.005 A*24:88 0.005 B57 B*57:01 0.005 DRB1*08:23 0.005 A*26:18 0.005 B58 B*58:01 0.579 D.843 0.005 A*31:11 0.005 B59 B*59:01 2.043 B60 B*40:07 0.010 B*40:52 0.005 B61 B*40:02 7.945 B*40:06 4.791 B*40:50 0.016 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005	Indefined	Δ*24.46	0.010				D00	B*55.04	2.040	DR17	DRB1*03:01	0.037
A*145 0.005 B50 B 500 0.005 DRB1*08:23 0.005 A*26:18 0.005 B58 B*58:01 0.579 A*31:11 0.005 B59 B*59:01 2.043 B60 B*40:01 5.348 B*40:07 0.010 B*40:52 0.005 B61 B*40:02 7945 B*40:03 0.407 B*40:50 0.016 B*40:50 0.016 B*40:53 0.005	ondenned	Δ*11·43	0.005				856	B*56.01	0.850	undefined	DBB1*04:57	0.005
A*26:18 0.005 A*31:11 0.005 B58 B*58:01 0.579 A*31:11 0.005 B60 B*40:01 5.348 B*40:07 0.010 B*40:52 0.005 B61 B*40:02 7945 B*40:06 4.791 B*40:03 0.407 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005		A*24·88	0.005				B50	B*57.01	0.005	undennied	DRB1*08.23	0.005
A*31:11 0.005 B59 B*59:01 2.043 B60 B*40:01 5.348 B*40:07 0.010 B*40:52 0.005 B61 B*40:02 7.945 B*40:06 4.791 B*40:03 0.407 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005		A*26.18	0.005				B58	B*58:01	0.579		00.20	0.000
B60 B*40:01 5.348 B60 B*40:07 0.010 B*40:52 0.005 B61 B*40:02 7.945 B*40:06 4.791 B*40:03 0.407 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005		A*31·11	0.005				B59	B*59:01	2 043			
B*40:07 0.010 B*40:52 0.005 B61 B*40:02 7.945 B*40:06 4.791 B*40:03 0.407 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005			0.000				B60	B*40:01	5.348			
B*40:52 0.005 B61 B*40:02 7.945 B*40:06 4.791 B*40:03 0.407 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005								B*40:07	0.010			
B61 B*40:02 7.945 B*40:06 4.791 B*40:03 0.407 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005								B*40:52	0.005			
B*40:06 4.791 B*40:03 0.407 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005							B61	B*40:02	7.945			
B*40:03 0.407 B*40:50 0.016 B*40:53 0.005 B*40:11 0.005								B*40:06	4.791			
B*40:50 0.016 B*40:53 0.005 B*40:11 0.005								B*40:03	0.407			
B*40:53 0.005 B*40:11 0.005								B*40:50	0.016			
B*40:11 0.005								B*40:53	0.005			
								B*40:11	0.005			

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Table 2 Continued

HLA-A serological specificity	HLA-A allele	GF (%)	HLA-C serological specificity	HLA-C allele	GF (%)	HLA-B serological specificity	HLA-B allele	GF (%)	HLA-DRB1 serological specificity	HLADRB1 allele	GF (%)
						B62	B*15:01	7.585			
							B*15:07	0.652			
							B*15:27	0.109			
							B*15:28	0.016			
							B*15:35	0.016			
							B*15:25	0.010			
							B*15:38	0.005			
						B64	B*14:01	0.016			
						B65	B*14:02	0.010			

B67

B71

B75

B77

B78

B81

Unknown^b

Null

undefined

B*67:01

B*15:18

B*15:11

B*15:02

B*15:13

B*78:02

B*81:01

B*54.21b

B*15:26N

B*35.64

B*51:36

B*52:05

B*52:11

1.225

1.522

0.881

0.031

0.005

0.005

0.005

0 0 0 5

0.005

0.005

0.005

0.005

0.005

GF, gene frequencies; HLA, human leucocyte antigen.

^aGF are calculated by using 19,183 haplotypes counted manually. Nomenclature of serological specificities, refer to *Tissue Antigens* 2010: 75: 291–455 (15)

^bThe allele is not in the paper (15).

Statistical analysis

The haplotypes were counted manually using Microsoft Excel® spreadsheets. The haplotypes that extended three or more generations were counted once (Figure 1). The allele and haplotype frequencies were calculated by using 19,183 haplotypes, counted as mentioned above. Relative LD values (RD) were computed for each haplotypes (17, 18). The exact test for deviation from Hardy-Weinberg Equilibrium were evaluated by GENEPOP software, version 4.2 (19, 20), which uses a Markov Chain (MC) algorithm (dememorization = 10,000, batches = 10,000, and iterations per batch = 10,000) to estimate the P-value.

The expected prevalence (P) of the allele or the haplotype under Hardy-Weinberg proportions were calculated from AF by using the following equation: $P = 1 - (1 - AF)^2$.

Results

HLA-A, -B, -C, and -DRB1 AF

Table 2 presents the list of the AF of HLA-A, -B, -C, and -DRB1 loci (21). We identified 44 HLA-A, 75 HLA-B, 29 HLA-C, and 42 HLA-DRB1 alleles and found A*24:02 to be 36.48%, the highest in Japanese population; thus, it is distributed in approximately 60% of the population. The alleles underlined in Table 2 need specific attention for HLA allele matching in unrelated HSCT between the Japanese, as they are present at high frequencies within a serotype (allele family) match.

Haplotype segregation analysis based on family study Haplotype frequencies of HLA-A-C-B-DRB1

Table 3 lists 60 haplotypes with frequencies higher than 0.2% in the population. Approximately, 38% of the entire Japanese population is expected to carry one or two of the five most common haplotypes.

These data have also been submitted to Allele Frequency Net Database (AFND) (22). The four-loci haplotypes with frequencies equal to or more than 0.01% and the AF can be found at the AFND website, www.allelefrequencies.net (22).

HLA-A-B-DRB1 haplotype sets with the same serotypes

Table 4 lists the sets of three-loci haplotypes at frequencies of 0.2% or greater, which would have the same serotype.

Haplotype frequencies of HLA-C-B

Table 5 lists 64 haplotypes with frequencies higher than 0.1 % in the population. Half of these haplotypes have RD values

Table 2					f	in 1	
lable 3	TLA-A-	C-D-	UNDI	napiotype	riequencies	III J	apanese-

N.	Ikeda	et al.

A–C–B–DRB1	HF (%)	RD	A-C-B-DRB1	HF (%)	RD
A*24:02-C*12:02-B*52:01-DRB1*15:02	8.377	0.79	A*02:07-C*01:02-B*46:01-DRB1*09:01	0.308	0.09
A*33:03-C*14:03-B*44:03-DRB1*13:02	4.473	0.75	A*33:03-C*03:02-B*58:01-DRB1*13:02	0.308	0.54
A*24:02-C*07:02-B*07:02-DRB1*01:01	3.722	0.66	A*26:01-C*03:03-B*35:01-DRB1*04:10	0.302	0.14
A*24:02-C*01:02-B*54:01-DRB1*04:05	2.539	0.33	A*02:01-C*03:03-B*15:11-DRB1*09:01	0.292	0.33
A*02:07-C*01:02-B*46:01-DRB1*08:03	1.866	0.54	A*24:02-C*04:01-B*15:01-DRB1*04:06	0.292	0.09
A*11:01-C*04:01-B*15:01-DRB1*04:06	1.345	0.40	A*24:02-C*14:02-B*51:01-DRB1*14:03	0.276	0.17
A*24:02-C*01:02-B*59:01-DRB1*04:05	1.058	0.51	A*24:02-C*03:04-B*40:01-DRB1*04:05	0.266	0.04
A*11:01-C*01:02-B*54:01-DRB1*04:05	1.001	0.13	A*26:02-C*03:03-B*15:01-DRB1*14:06	0.261	0.20
A*26:01-C*03:04-B*40:02-DRB1*09:01	0.745	0.10	A*24:02-C*03:04-B*40:02-DRB1*04:05	0.255	0.03
A*24:02-C*08:01-B*40:06-DRB1*09:01	0.709	0.14	A*02:01-C*07:02-B*07:02-DRB1*01:01	0.250	0.04
A*24:02-C*14:02-B*51:01-DRB1*09:01	0.652	0.09	A*02:06-C*07:02-B*07:02-DRB1*01:01	0.250	0.04
A*31:01-C*14:02-B*51:01-DRB1*08:02	0.579	0.14	A*11:01-C*01:02-B*54:01-DRB1*08:03	0.240	0.03
A*33:03-C*14:03-B*44:03-DRB1*08:03	0.547	0.08	A*11:01-C*01:02-B*55:02-DRB1*04:05	0.240	0.09
A*26:02-C*08:01-B*40:06-DRB1*09:01	0.542	0.30	A*31:01-C*14:02-B*51:01-DRB1*04:05	0.240	0.03
A*02:01-C*03:04-B*13:01-DRB1*12:02	0.532	0.45	A*02:01-C*15:02-B*51:01-DRB1*15:01	0.235	0.08
A*24:02-C*01:02-B*46:01-DRB1*08:03	0.532	0.11	A*03:01-C*05:01-B*44:02-DRB1*13:01	0.235	0.63
A*02:06-C*08:01-B*40:06-DRB1*09:01	0.464	0.10	A*11:01-C*07:02-B*67:01-DRB1*15:01	0.235	0.19
A*11:01-C*07:02-B*39:01-DRB1*08:03	0.433	0.13	A*24:02-C*14:03-B*44:03-DRB1*13:02	0.235	0.04
A*26:01-C*03:04-B*40:02-DRB1*08:02	0.427	0.10	A*01:01-C*06:02-B*37:01-DRB1*10:01	0.229	0.57
A*02:06-C*03:03-B*35:01-DRB1*15:01	0.422	0.05	A*24:02-C*03:03-B*35:01-DRB1*15:01	0.229	0.03
A*24:02-C*12:02-B*52:01-DRB1*09:01	0.391	0.03	A*24:02-C*03:04-B*40:01-DRB1*11:01	0.229	0.09
A*31:01-C*14:02-B*51:01-DRB1*14:03	0.391	0.25	A*31:01-C*14:02-B*51:01-DRB1*09:01	0.229	0.03
A*02:06-C*07:02-B*39:01-DRB1*15:01	0.386	0.12	A*26:03-C*03:03-B*15:01-DRB1*09:01	0.224	0.10
A*24:02-C*03:04-B*40:02-DRB1*09:01	0.370	0.04	A*02:06-C*01:02-B*54:01-DRB1*04:05	0.219	0.03
A*02:01-C*01:02-B*54:01-DRB1*04:05	0.360	0.05	A*02:06-C*03:03-B*35:01-DRB1*09:01	0.219	0.02
A*26:03-C*03:03-B*15:01-DRB1*15:01	0.344	0.15	A*02:01-C*01:02-B*46:01-DRB1*08:03	0.214	0.04
A*11:01-C*07:02-B*67:01-DRB1*16:02	0.339	0.38	A*02:01-C*08:01-B*40:06-DRB1*09:01	0.214	0.04
A*02:06-C*01:02-B*59:01-DRB1*04:05	0.323	0.16	A*02:06-C*08:01-B*48:01-DRB1*04:07	0.214	0.37
A*24:02-C*03:03-B*15:07-DRB1*04:03	0.323	0.50	A*31:01-C*04:01-B*56:01-DRB1*09:01	0.214	0.25
A*24:02-C*07:04-B*15:18-DRB1*04:01	0.318	0.34	A*31:01-C*07:02-B*07:02-DRB1*01:01	0.209	0.04

HF, haplotype frequencies; HLA, human leucocyte antigen; RD, relative linkage disequilibrium value.

^aFour-locus haplotypes with HF >0.2% are listed.

Table 4	Haplotype	sets assigned	same serotype	of HLA-A	-B-DRB1 ^a
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Set no.	Haplotype	HF (%)
1	A*02:01-B*07:02-DRB1*01:01	0.26
	A*02:06-B*07:02-DRB1*01:01	0.25
2	A*02:01-B*46:01-DRB1*08:03	0.23
	A*02:07-B*46:01-DRB1*08:03	1.87
3	A*02:01-B*54:01-DRB1*04:05	0.38
	A*02:06-B*54:01-DRB1*04:05	0.22
4	A*02:01-B*40:06-DRB1*09:01	0.29
	A*02:06-B*40:06-DRB1*09:01	0.48
5	A*24:02-B*40:02-DRB1*09:01	0.53
	A*24:02-B*40:06-DRB1*09:01	0.95
6	A*24:02-B*15:01-DRB1*04:06	0.31
	A*24:02-B*15:07-DRB1*04:03	0.34
7	A*24:02-B*35:01-DRB1*04:03	0.23
	A*24:02-B*35:01-DRB1*04:05	0.22
8	A*26:01-B*40:02-DRB1*09:01	0.81
	A*26:01-B*40:06-DRB1*09:01	0.22
	A*26:02-B*40:06-DRB1*09:01	0.54

HF, haplotype frequency; HLA, human leucocyte antigen.

^aThe analysis objects are HF with more than 0.2%.

more than 0.7, suggesting conservation of HLA-C-B linkage. B*40:02 and B*40:06 which correspond to the same serotype (B61) have high frequencies alleles of B61 and need attention for matching in HSCT. Focusing on these, Table 5 shows the frequency of C*03:04-B*40:02 as 6.26%, while the frequency of B*40:02 is 7.95% (Table 2); therefore, the frequency of C*03:04-B*40:02 linkage would account for 79% of B*40:02 alleles. Similarly, linkage of B*40:06 with C*08:01 would account for 81% of the presence of B*40:06. Thus, it is important to differentiate serotypes such as B61 when the constituting alleles are in linkage with different HLA-C alleles.

Observed recombination

A total observation number of recombination events were 136 in 134 families. These were divided into two groups: (i) the haplotypes of 103 parents (75.7%) could be determined, (ii) the haplotypes of 33 parents (24.3%) could not be determined and thus were inferred. Table 6 summarizes the observation number of recombination events in informative families which contain the parents and three or more children. The genotypes

HLA allele	and	haplotype	frequency	י in נ	Japanese	population
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Table 5	HLA-C-B	haplotype	frequencies	in Japanese ^a
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C-B	HF (%)	RD	C-B	HF (%)	RD
C*12:02-B*52:01	10.963	0.99	C*08:01-B*15:18	0.495	0.27
C*01:02-B*54:01	7.147	0.94	C*03:04-B*51:01	0.469	-0.58
C*14:02-B*51:01	6.761	0.98	C*04:01-B*35:01	0.464	0.02
C*14:03-B*44:03	6.641	0.99	C*04:01-B*40:01	0.464	0.05
C*03:04-B*40:02	6.256	0.76	C*03:04-B*40:03	0.396	0.97
C*03:03-B*35:01	6.115	0.70	C*05:01-B*44:02	0.370	0.99
C*07:02-B*07:02	5.573	0.99	C*03:04-B*35:01	0.339	-0.67
C*01:02-B*46:01	4.316	0.89	C*03:04-B*40:06	0.339	-0.43
C*08:01-B*40:06	3.904	0.80	C*15:02-B*40:06	0.334	0.06
C*07:02-B*39:01	3.196	0.96	C*01:03-B*46:01	0.318	1.00
C*03:03-B*15:01	3.190	0.33	C*07:02-B*39:02	0.308	1.00
C*03:04-B*40:01	2.867	0.47	C*15:02-B*40:02	0.292	0.02
C*04:01-B*15:01	2.606	0.56	C*06:02-B*13:02	0.287	1.00
C*01:02-B*55:02	2.252	0.82	C*07:02-B*38:02	0.276	0.98
C*01:02-B*59:01	2.012	0.98	C*03:04-B*15:01	0.266	-0.72
C*08:01-B*48:01	1.553	0.50	C*03:03-B*55:02	0.261	-0.25
C*15:02-B*51:01	1.345	0.38	C*03:03-B*48:01	0.240	-0.36
C*07:02-B*67:01	1.220	1.00	C*01:02-B*56:01	0.235	0.12
C*03:04-B*13:01	1.069	0.90	C*03:03-B*40:01	0.235	-0.66
C*08:01-B*35:01	1.069	0.07	C*08:03-B*54:01	0.229	0.10
C*03:03-B*40:02	1.048	0.00	C*01:02-B*51:01	0.224	-0.86
C*07:02-B*40:01	0.923	0.05	C*07:02-B*39:04	0.209	1.00
C*08:03-B*48:01	0.923	0.67	C*01:02-B*56:03	0.177	1.00
C*07:04-B*15:18	0.907	0.98	C*15:02-B*51:02	0.151	0.63
C*03:03-B*15:11	0.850	0.96	C*01:02-B*40:02	0.141	-0.90
C*15:02-B*40:01	0.704	0.18	C*12:02-B*27:04	0.141	0.72
C*01:02-B*15:01	0.626	-0.53	C*15:02-B*15:01	0.141	-0.40
C*03:03-B*15:07	0.610	0.93	C*08:03-B*15:01	0.136	0.03
C*03:02-B*58:01	0.568	1.00	C*03:03-B*55:04	0.120	0.91
C*04:01-B*56:01	0.537	0.61	C*07:02-B*40:02	0.115	-0.89
C*07:02-B*15:01	0.500	-0.48	C*04:01-B*15:27	0.109	1.00
C*06:02-B*37:01	0.495	1.00	C*04:01-B*48:01	0.109	-0.14

HF, haplotype frequencies; HLA, human leucocyte antigen; RD, relative linkage disequilibrium value.

 $^{\rm a}$ C-B haplotypes with HF >0.1% are listed.

 Table 6
 Number of HLA–A/C, C/B, B/DRB1 recombination evens by each family structure

	Number of children	Number of families	A/Cª n (%R/T)	B/DRB1ª n (%R/T)	A/DRB1ª n (%R/T)
Parents	5	5	b	b	b
	4	28	2 (0.89)	1 (0.45)	3 (1.34)
	3	233	7 (0.50)	8 (0.57)	15 (1.07)
Total	836	266	9 (0.54)	9 (0.54)	18 (1.08)

HLA, human leucocyte antigen.

 $^aX\!/Y$, number of recombination between X and Y; %R/T, % of recombination per transmission.

^bNo observation of recombination.

of these parents are heterozygote at all loci of HLA-A, -B, -C, and -DRB1. Group (ii) is not included in these informative families. The transmission of recombination (%R/T) shows the HLA-A-DRB1 recombination probability as 1.08% per child. Furthermore, Table 6 also indicates the recombination probabilities of HLA-A-C and B-DRB1 are 0.54%.

Comparison to the result by MLE

Table 7 shows the haplotype frequencies of HLA-A-C-B-DRB1 based on family study (result-FS) and based on MLE (result-MLE) with frequencies more than 0.5%. In the frequent haplotypes with frequencies not less than 0.12%, result-MLE tends to be higher than result-FS. In the low-frequent haplotypes with less than 0.12%, result-MLE tends to be lower than result-FS. In addition, result-MLE could not be detected in 585 haplotypes of the 2099 haplotypes with frequencies less than 0.12% in result-FS.

On the allele data used for this comparison, four loci showed Hardy–Weinberg Equilibrium: the *P*-values of the exact test at HLA-A, -B, -C, and DRB1 loci were 0.3184, 0.2557, 0.1449, and 0.4998, respectively.

Discussion

The AF presented in Table 2 show the high frequency of A*24:02 at 36.48%; therefore, around 60% of the population could be administered peptide vaccines such as WT1 peptide

Table 7 Comparison to maximum likelihood estimation $(n = 4500)^a$

A-C-B-DRB1	FS (%)	MLE (%)
A*24:02-C*12:02-B*52:01-DRB1*15:02	8.144%	8.298%
A*33:03-C*14:03-B*44:03-DRB1*13:02	4.444%	4.478%
A*24:02-C*07:02-B*07:02-DRB1*01:01	3.689%	3.857%
A*24:02-C*01:02-B*54:01-DRB1*04:05	2.344%	2.490%
A*02:07-C*01:02-B*46:01-DRB1*08:03	2.044%	2.053%
A*11:01-C*04:01-B*15:01-DRB1*04:06	1.322%	1.326%
A*24:02-C*01:02-B*59:01-DRB1*04:05	1.100%	1.167%
A*11:01-C*01:02-B*54:01-DRB1*04:05	0.833%	0.815%
A*26:01-C*03:04-B*40:02-DRB1*09:01	0.778%	0.892%
A*24:02-C*08:01-B*40:06-DRB1*09:01	0.733%	0.830%
A*24:02-C*14:02-B*51:01-DRB1*09:01	0.722%	0.803%
A*31:01-C*14:02-B*51:01-DRB1*08:02	0.589%	0.619%
A*33:03-C*14:03-B*44:03-DRB1*08:03	0.578%	0.589%
A*26:02-C*08:01-B*40:06-DRB1*09:01	0.556%	0.526%
A*24:02-C*01:02-B*46:01-DRB1*08:03	0.522%	0.504%
A*02:01-C*03:04-B*13:01-DRB1*12:02	0.511%	0.502%

FS, haplotype frequencies based on family study; MLE, haplotype frequencies estimated by maximum likelihood estimation.

^aFour-locus haplotypes with frequencies >0.5% in result-FS are listed.

vaccine presented by HLA molecules coded A*24:02 (23, 24). Moreover, around 80% of the population could be administered the vaccines (25, 26) presented by HLA molecules coded by one of three alleles as A*24:02 (36.5%), A*02:01 (11.6%), and A*02:06 (9.1%).

The haplotype frequencies are also characteristic of Japanese population. The haplotypes of high frequencies are well conserved. Approximately one third (38%) of Japanese population carry the five most common haplotypes. We believe that this is strongly influenced by the founder effect: the ancestors having the common haplotypes migrated to Japan, thus, their haplotypes have been concentrated. While searching in the AFND (22), we found that the common haplotypes are homologous to those residing in the neighboring countries, especially in South Korea (11, 12, 27-31). In Korean population, the frequent haplotypes are similar to the ones in Japanese population. The three major Japanese haplotypes A*24:02-C*12:02-B*52:01-DRB1*15:02, A*33:03-C*14:03-B*44:03-DRB1*13:02, and A*24:02-C*07:02-B*07: 02-DRB1*01:01 have also high frequencies in Korea (1.9%, 4.2%, 2.9%, respectively) (27), suggesting the migration of some ancestors though the Korean Peninsula.

The haplotype analysis not only helps in understanding the history of human migration but also in matching for unrelated donor searches for HSCT. In JMDP, the HLA compatibility with a donor is evaluated by both serotype and genotype. Furthermore, allele matching is a better evaluation of compatibility compared to the serotype matching; the rejection and GVHD risk of bone marrow transplant (BMT) have been found to be lower with allele-level matching compared to the serotype-level matching (3, 32). Accordingly, focusing on the alleles in every serotype, A2, A26, etc. increases the possibility of allele mismatch in spite of serotype match (Table 2). As

shown in Table 4, HLA-A2, B61, B15, and DR4 especially increase the allele mismatch risk. However, compared with South Korean haplotype analysis, South Korea has 15 sets of haplotypes to pay attention to in HSCT matching (27) but Japan has eight sets (Table 4). It also shows that for most HLA haplotypes at the serotype-level, HLA haplotype matching is almost allele-level matching in HSCT between the Japanese.

Although HLA-C locus is not indispensable for registering information in HSCT, HLA-C allele matching is important (32, 33). Even without information of donor HLA-C allele, the C-B haplotypes can predict HLA-C allele, although not always, because of well-conserved C-B linkage (Table 5); the conservation is possible due to short genetic linkage distance. In other words, HLA-B allele matching increases the possibility of HLA-C allele matching. Accordingly, analysis in the HLA distribution in Japanese population may contribute in planning the strategies of HLA matching for HSCT.

Result-MLE was similar to result-FS (Table 7). Table 7 indicates the haplotype frequencies estimated by the software are very similar to real family-derived haplotypes. If the detection of the low frequency haplotypes is needed, determination of haplotypes by descent or a large sample size appears to be necessary.

In conclusion, this study of determination of HLA allele and haplotype frequencies using family samples not only serves as a tool for elucidating linkage of each HLA locus but also acts as a tool in detecting HLA gene mutations in human germ cells such as recombination. The data obtained in this study will be useful in various fields such as anthropology, transplantation therapy, and disease association studies.

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Conflicts of interest

The authors have no conflicts of interest.

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