

ORIGINAL ARTICLE

Distribution of the minor histocompatibility antigens in Korean population and disparities in unrelated hematopoietic SCT

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Minor histocompatibility antigens (mHags) are polymorphic peptides presented to T lymphocytes restricted by the MHC molecule. It has been reported that disparities of mHags are a potential risk factor for GVHD after hematopoietic SCT (HSCT). Here we observed allelic frequencies of HA-1, -2 and -8 in 139 Korean healthy individuals using PCR-sequence-specific primers, and analyzed the correlation between disparity of these mHags and acute GVHD (aGVHD) in 54 patients who underwent HSCT from unrelated HLA-identical donors. The allelic frequencies in Korean healthy individuals were 39.6 and 60.4% for HA-1^H and HA-1^R, 92.4 and 7.6% for HA-2^M and HA-2^V, 36.7 and 63.3% for HA-8^R and HA-8^P, respectively. The frequencies of mHags incompatibility known to be associated with aGVHD were 16.7% in HA-1, 0% in HA-2 and 25.9% in HA-8. However, the statistically significant association of aGVHD with these mHags incompatibility was not found between healthy donors and leukemia patients after unrelated HSCT. This first report about mHags in Koreans may be helpful in further defining the clinical impact of mHags disparities in HSCT and in comparing with other populations.

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Introduction

GVHD as one of the major drawbacks of allogeneic hematopoietic SCT (allogeneic HSCT) occurs in 20–40%, even if the donor and recipient have identical HLA antigens.¹ Minor histocompatibility antigens (mHags) are

peptides derived from polymorphic intracellular proteins presented by HLA class I or class II molecules on the cell membrane and recognized as alloantigens by T cells between HLA-matched individuals.² The first report on mHag-mediated immune response in human transplantation demonstrated an observation wherein a female patient rejected bone marrow transplanted from her HLA-identical brother.³ Then the correlation between the mismatches of mHag after HLA-identical sibling donor bone marrow transplantation and the development of acute GVHD (aGVHD) was examined via CTL assays.⁴

Defining the polymorphisms of mHags and the tissue distribution has been studied to confirm the association between GVHD and mHags and reduce GVHD activity after HSCT.⁵ HA-1, -2 and -8 have been reported to play a prognostic factor for an increased risk of aGVHD after allogeneic HSCT.^{4,6} HA-1 (*HMHA1*, rs376453 and rs1801284) is an HLA-A*0201 or HLA-B*60-restricted nonapeptide from a protein encoded by a gene termed *KIAA0223*, located on chromosome 19p13.3, which has two known alleles differing at positions 500 and 504 of the cDNA sequence.^{7,8} This antigen has two allelic variants: the HA-1^H allele characterized by the presence of histidine at position 3 of the nonapeptide (VLHDDLLEA) and the HA-1^R allele encoding arginine at the same position (VLRDDLLEA).⁷ The HA-2 encoded by the novel human class I myosin gene (*MYOIG*), located on the short arm of chromosome 7 consists of two alleles, YIGEVLVSV (HA-2^V) and YIGEVLVSM (HA-2^M), and presented by HLA-A*0201.⁹ The HA-8 (*KIAA0020*, rs2173904) was found to be a product of polymorphism at position 864 of the *KIAA0020* gene located on chromosome 9p, and this gene encodes either RTLDKVLEV (HA-8^R) or PTLDKVLEV (HA-8^P). The HA-8 gene-encoded peptides are recognized by CTLs, which react to HLA-A*0201.¹⁰ To sum up, mHags HA-1, -2 and -8 are encoded by biallelic loci, with immunogenic variants, HA-1^H, HA-2^V and HA-8^R, which induce strong HLA-A2-restricted alloreactive T-cell responses, and nonimmunogenic counterparts, HA-1^R, HA-2^M and HA-8^P, which represent functional null alleles.

We determined the genotype of HA-1, -2 and -8 in 139 Korean healthy individuals using PCR-sequence-specific primers (PCR-SSP)¹¹ and compared with that of other

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population because this is the first report about mHags in Koreans. The correlation between aGVHD and disparity of these mHags was also evaluated in 54 Korean patients who underwent HSCT from unrelated HLA-identical donors.

Materials and methods

Subjects

Genotypes and allele frequencies for mHags were determined using genomic DNA obtained from 139 healthy Koreans and 54 donor-recipient pairs who underwent unrelated HSCT. The recipients underwent unrelated HSCT at The Catholic Hematopoietic Stem Cell Transplantation Center between January 2004 and February 2006 for hematologic diseases. The healthy normal group consisted of staffs and students of College of Medicine, The Catholic University of Korea. Table 1 shows the characteristics of the patients included in the study.

PCR-SSP for mHags

Genomic DNA was isolated from whole blood using an AccuPrep Genomic DNA Extraction kit (Bioneer Corporation, Daejeon, Korea), according to the manufacturer's instructions. DNA concentration was adjusted to 50 ng/ μ l and used as templates for typing of mHags.

Table 1 Clinical characteristics of the patient/donor pairs included in this study ($n = 54$)

Patient's age (median, range)	23 (1–51)
Donor's age (median, range)	29 (21–40)
Patient's sex (male/female)	30:24
Donor's sex (male/female)	41:13
Donor/recipient gender combination (patient/donor)	Male/male 23 Male/female 7 Female/male 18 Female/female 6
Diagnoses and disease status	
Acute myelogenous leukemia	21
First remission/ \geq second remission	20:1
Acute lymphoblastic leukemia	10
First remission/ \geq second remission	8:2
Severe aplastic anemia	10
Chronic myelogenous leukemia	8
First chronic phase/other phase	6:2
Myelodysplastic syndrome	5
RAEB/RAEBt/CMML	2:2:1
Source of stem cells (PB/BM)	8:46
T-cell depletion, <i>ex vivo</i>	None
GVHD prophylaxis	
Tacrolimus + MTX	38
CsA + MTX	16
Conditioning regimen	
TBI + CY	30
Busulfan + CY	18
Others	6

Abbreviations: CMML = chronic myelomonocytic leukemia; MTX = short-term methotrexate; PB = peripheral blood; RAEB = refractory anemia with excess of blasts; RAEBt = refractory anemia with excess of blasts in transformation.

DNA was amplified for HA-1, -2 and -8 by PCR using allele-specific forward primers and reverse common primers (Table 2). Two different primer sets were designed so that each contained a common primer and specific primer for the HA-1, -2 and -8 alleles. Amplification with these primers for HA-1, -2 and -8 alleles resulted in 179, 203 and 257 bp fragments, respectively (Figure 1). A PCR was performed in a total volume of 20 μ l containing 50 ng of genomic DNA, 0.5 μ M of each mHag-specific primer and reverse common primers, 0.075 μ M of internal control primers, TDMH (10 \times PCR buffer (670 mM Tris base, 166 mM ammonium sulfate, 1% Tween-20), 25 mM dNTP, 25 mM MgCl₂, distilled H₂O), 1 U Taq-polymerase (Intron Biotechnology, Seongnam, Korea). Amplification was performed in a Bio-Rad My Cycler (Bio-Rad, Hercules, CA, USA): 1 cycle at 95°C for 40s; 10 cycles of denaturation at 95°C for 30s, annealing at 62°C for 40s, extension at 72°C for 30s, 25 cycles of denaturation at 95°C

Table 2 Primer sets for genotyping of HA-1, -2 and -8

Primer	Sequence (5'-3')
HA-1 ^H forward	ACTTAAGGAGTGTGTGCTGCA
HA-1 ^R forward	ACTTAAGGAGTGTGTGTTGCG
HA-1 reverse	CCTCAGAGCCTTAGCTGTCA
HA-2 ^V forward	GCTCCTGGTAGGGGTTTAC
HA-2 ^M forward	GCTCCTGGTAGGGGTTTCAT
HA-2 reverse	CTTCTTCTCCACTCTCAGC
HA-8 ^R forward	TCTAACACTTTGTCCAGAGTTC
HA-8 ^P forward	TCTAACACTTTGTCCAGAGTTG
HA-8 reverse	ACTTGGTTGGCCTGGCTCTT
Internal ^a forward	CCTTCCAACCATTCCTTA
Internal ^a reverse	GTCCATGTCCTTCTGAAGCA

^a*Homosapiens growth hormone 2 (GH2) gene (NM_022557).*

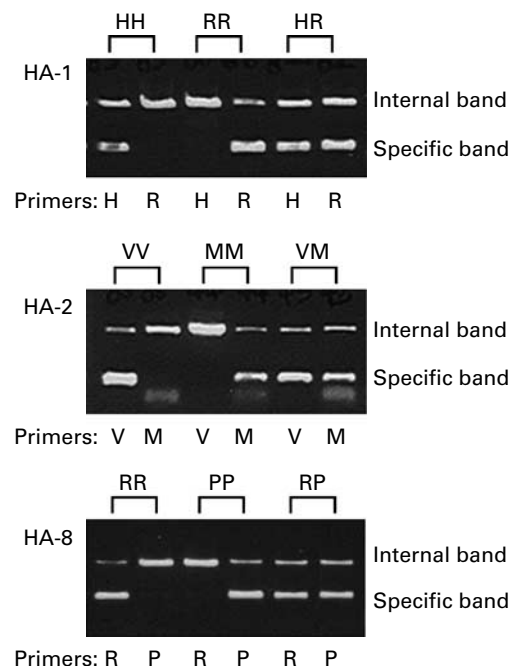


Figure 1 Genotyping of HA-1, -2 and -8 by PCR-sequence-specific primers (PCR-SSP).

for 30 s, annealing at 57°C for 40 s, extension at 72°C for 30 s and final extension at 72°C for 7 min. The PCR products were analyzed by electrophoresis on a 1.5% agarose gel. The standard samples for HA-1, -2 and -8 typing by PCR-SSP were confirmed by cloning and nucleotides sequencing.

Statistical analysis

The allele frequencies were counted by excel program. Any statistical significance of differences between groups was tested by χ^2 analysis when test samples are more than five or by two-tailed Fisher's exact test when test samples are less than five. *P*-values less 0.05 were considered to be statistically significant.

Results

Distribution of mHags frequencies in Korean population

The frequencies of the HA-1, -2 and -8 alleles defined in the samples of 139 healthy unrelated individuals from Korea were typed (Table 3). The HA-1 genotype frequencies in total subjects were HA-1^{H/H} 12.9%, HA-1^{R/R} 33.9% and HA-1^{H/R} 53.2%. As the HA-1 antigen presentation is restricted by HLA-A*02 or HLA-B*60, HLA-A*02-positive or HLA-B*60-positive samples were selected to confirm distribution of HA-1 genotype. The genotype distribution in the total group was not statistically different from the genotype distribution in the HLA-A*02-positive or HLA-B*60-positive group. For HA-2, HA-2^{V/V} genotype frequency of 86.3% was much higher than other genotype frequencies of HA-2. There were only two HA-2^{M/M} genotype-positive samples in total. The genotype frequencies of HA-8^{R/R}, HA-8^{R/P} and HA-8^{P/P} were 15.1, 43.1 and 41.8%, respectively. Since HA-2 and HA-8 antigen presentation is also restricted by HLA molecules, only HLA-A*02-positive samples were selected to observe distribution of genotype for each mHag, and both of them were not statistically different from the genotype distribution in the total group.

Table 3 Genotype frequencies of HA-1, -2 and -8 alleles in healthy Korean

Locus	Genotype	Total, n (%) (n = 139)	HLA-A*02 or HLA-B*60, n (%) (n = 77)
HA-1	H/H	18 (12.9)	7 (9.1)
	H/R	74 (53.2)	44 (57.1)
	R/R	47 (33.9)	26 (33.8)
HA-2	V/V	120 (86.3)	65 (87.8)
	V/M	17 (12.2)	9 (12.2)
	M/M	2 (1.5)	0 (0)
HA-8	R/R	21 (15.1)	10 (13.5)
	R/P	60 (43.1)	38 (51.4)
	P/P	58 (41.8)	26 (35.1)

Comparison of mHag frequencies among different population

The allelic frequency observed for HA-1 variants in this study was compared with those reported by others in Japanese,¹² Caucasian,¹³ Spanish¹⁴ and Italian populations¹⁵ (Table 4). The allelic frequency of the HA-1 in Koreans was only different from that in Italians among four different populations (*P* < 0.0048; OR: 1.58, 95% CI: 1.14–2.17). Although the allelic frequency of HA-1 in the Korean population was not statistically different from that in the Caucasian population (*P* = 0.45), significant differences were observed in the allelic frequencies of HA-2 (*P* < 1.4 × 10⁻⁵; OR: 2.89, 95% CI: 1.76–4.74) and -8 (*P* = 0.035; OR: 0.73, 95% CI: 0.53–0.97). For the allelic frequency of HA-2, the HA-2^M allelic frequencies in the Caucasian and Italian populations were about three times (*P* < 1.4 × 10⁻⁵; OR: 2.89, 95% CI: 1.76–4.74) and twice (*P* = 0.0028; OR: 2.43, 95% CI: 1.37–4.29) higher than that in Koreans.

Disparities of mHags between healthy donors and leukemia patients

Table 5 summarizes the distribution of HA-1, -2 and -8 incompatibility between 54 leukemia patients and their HLA-identical donors. Since no HLA-B*60-positive sample was found in the 54 pairs, it was excluded from the list for HA-1. For HA-1, -2 and -8, the risk of GVHD due to disparities in mHags is increased in the combination of mHag-positive recipient and mHag-negative donor, because one allele of these mHags can be considered as a null allele in terms of T-cell reactivity.^{7,9,10} The combination of mHag-positive recipient and mHag-negative donor (recipient mHags-incompatible pair) for HA-1, -2 and -8 was 24.1, 0 and 37% in total Korean samples. The frequency of HLA-A*02-positive samples that restrict presentation of HA-1, -2 and -8 was 57.4% of total samples. Therefore, in the context of HLA restriction, the percentages that reflect the possibility of exploiting GVHD targeted against HA-1, -2 or -8 were 16.7, 0 and 25.9% of the cases (data not shown).

We also studied the incidence of aGVHD among the different donor–recipient pairs' phenotype combinations of HA-1, -2 or -8 in all patients group, HLA-A*02-positive group and HLA-A*0201-positive group, respectively. For HA-1 and HA-8, the percentage of developing grade II–IV aGVHD in each mHag incompatible patients was not significantly different in each mHag compatible patients in all three groups. In case of HA-2, there was not any combination of recipient HA-2 incompatibility. Thus, the correlation of HA-2 incompatibility with aGVHD could not be examined.

Discussion

Disparities in mHags between donor and recipient are known to increase the rates of aGVHD after HLA-identical sibling BMT,⁴ and the correlation between a single amino acid polymorphism of mHags and GVHD has been studied by many investigators. Recently, it has been reported that

Table 4 Allelic frequencies of HA-1, -2 and -8 in different population

Locus	Allele	Allelic frequency, n (%)				
		Korean ^a (n = 278)	Japanese ^b (n = 240)	Caucasian ^c (n = 518)	Spanish ^d (n = 406)	Italian ^e (n = 420)
HA-1	H	110 (39.6)	82 (34.2)	190 (36.7)	133 (32.8)	123 (29.3)
	R	168 (60.4)	158 (65.8)	328 (63.3)	273 (67.2)	297 (70.7)
	P-value	—	—	—	—	0.0048
Locus	Allele	Allelic frequency, n (%)				
		Korean ^a (n = 278)	Caucasian ^c (n = 518)	Italian ^e (n = 199)		
HA-2	V	257 (92.4)	419 (80.9)	166 (83.7)		
	M	21 (7.6)	99 (19.1)	33 (16.3)		
	P-value	—	$P < 1.4 \times 10^{-5}$	0.0028		
Locus	Allele	Allelic frequency, n (%)				
		Korean ^a (n = 278)	Caucasian ^c (n = 518)			
HA-8	R	102 (36.7)	230 (44.4)			
	P	176 (63.3)	288 (55.6)			
	P-value	—	0.035			

^aIn this study.^bReported in reference Bunce *et al.*¹¹^cReported in reference Murata *et al.*¹²^dReported in reference Pietz *et al.*¹³^eReported in reference Arostegui *et al.*¹⁴**Table 5** Distribution of HA-1, -2 and -8 incompatibility between healthy donors and leukemia patients in Korea

Locus	Genotypes		Allelic frequency n (%)	
	Donors	Recipients	Total (n = 54)	HLA-A*02- positive (n = 31)
HA-1	RR	HH	2 (3.7)	1 (3.2)
	RR	HR	11 (20.4)	8 (25.9)
HA-2	MM	VV	0 (0)	0 (0)
	MM	VM	0 (0)	0 (0)
HA-8	PP	RR	6 (11.1)	4 (12.9)
	PP	RP	14 (25.9)	10 (32.2)

the mHag-induced alloimmune response also causes the curative GVL effect, and mHag could be a target for immunotherapy after transplantation.^{16,17} To estimate the effect of mHags in the situations limited to recipient mHags-incompatible pairs, needs investigation of the distribution of mHag alleles in the normal population. However, to date, the frequencies of mHags have not been studied in the Korean population. Therefore, we examined the allelic distribution for HA-1, -2 and -8 in the Korean population, and compared it in other populations.

The allelic distribution for HA-1, -2 and -8 in the Korean population was found to be different from particular populations (Table 4). In the case of HA-1, the allelic distribution is similar among regional ethnics as shown among Asians (Korean and Japanese¹²) and Europeans

(Italian¹⁵ and Spanish¹⁴), in contrast to the allelic distribution between Korean and Italian population. Similar to HA-1, the allelic frequency of HA-2 in Koreans is significantly different from that in Caucasian¹³ and Italian populations,¹⁵ but no significant difference of the allelic frequency between Italian and Caucasian populations. Also, because a majority (>90%) of Koreans possesses immunogenic V alleles of HA-2, a very low probability of disparity for HA-2 could be suggested in Korean donor/recipient pairs of HLA-identical stem cell transplantation (Table 4).

Although the recognition of HA-1, -2 and -8 was HLA-A*0201-restricted, the analysis of association between HA-1, -2 or -8 incompatibility and incidence of aGVHD (grade II–IV) has been demonstrated in the context of either HLA-A2 or A*0201.^{4,6,12,18} The subtypes of HLA-A2 in Korean population consist of HLA-A*0201 (14.3%), A*0206 (7.7%) and rarely any other types,¹⁹ and HLA-A*0201 and A*0206 accounts for about 85%, and they belong to the A2-like supertype that is characterized by similar ligand specificity.²⁰ Thus, we investigated the correlation between HA-1,-2 or -8 incompatibility and developing of grade II–IV aGVHD in the context of both HLA-A2 and A*0201.

The association between HA-1, -2 or -8 incompatibility and the development of aGVHD in the context of HLA restriction did not show any statistical significance. One hypothesis to account for the absence of such a correlation in our group of donor–recipient pairs could be the considerable number of children patients. There were 24 pairs of adults and 20 pairs of children (age, ≤16 years) in

our group of patients. A previous report suggested that a mismatch of HA-1 was significantly correlated with aGVHD (grade II–IV) in adults but not in children.⁴ Also there was no significant association between a recipient HA-1 disparity and aGVHD in group of patients consisting of both adults and children.^{12,21,22} Therefore, it is possible that patients' age might affect the associations between these mHags incompatibility and aGVHD in case of HA-2 and -8.

In addition to the patient's age, there might be other possibilities to account for the absence of correlation such as other mHag incompatibilities and other not discovered mHags. For example, the HY antigen is sex-linked mHag which is only present in males, and the HY antigen is influential in occurrence of GVHD between male recipients and female donors.²³ Because there were only seven pairs mismatched for sex—male recipient and female donor—in this study, the association between HY incompatibility and aGVHD could not be analyzed.

The results of previous studies have suggested that the HA-1 and -2 antigens are restrictively expressed by hematopoietic cells and a limited number of solid tumors.^{7,8} Thus, HA-1 and -2 may be associated with induction of GVL effect rather than occurrence of severe aGVHD. In spite of these hematopoiesis-restricted expression of HA-1 and -2, the association between HA-1, and -2 incompatibility and the occurrence of GVHD may be explained as follows. Shortly after non-T-cell depletion, allogeneic HSCT APC are still of recipient origin and may induce an mHag-specific immune response directed primarily against these APCs and secondarily against neighboring tissues resulting in skin, liver and gastrointestinal GVHD. However, it is too early to draw any conclusion, because in our study there was only small number of donor/recipient pairs to be analyzed in the context of HLA restriction. Therefore, further study is needed to confirm the correlation between HA-1, -2 or -8 disparity and clinical outcomes including aGVHD and GVL in larger group of patients.

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References

- 1 Mullighan C, Heatley S, Doherty K, Szabo F, Grigg A, Hughes T *et al*. Non-HLA immunogenetic polymorphisms and the risk of complications after allogeneic hemopoietic stem-cell transplantation. *Transplantation* 2004; **77**: 587–596.
- 2 Spierings E, Wieles B, Goulmy E. Minor histocompatibility antigens—big in tumor therapy. *Trends Immunol* 2004; **25**: 56–60.
- 3 Goulmy E, Termijtelen A, Bradley BA, van Rood JJ. Alloimmunity to human H-Y. *Lancet* 1976; **2**: 1206.
- 4 Goulmy E, Schipper R, Pool J, Blokland E, Falkenburg JH, Vossen J *et al*. Mismatches for minor histocompatibility antigens between HLA-identical donors and recipients and

the development of graft versus host disease after bone marrow transplantation. *N Engl J* 1996; **334**: 281–285.

- 5 Warren EH, Gavin M, Greenberg PD, Riddell SR. Minor histocompatibility antigens as targets for T-cell therapy after bone marrow transplantation. *Curr Opin Hematol* 1998; **5**: 429–433.
- 6 Akatsuka Y, Warren EH, Gooley TA, Brickner AG, Lin MT, Hansen JA *et al*. Disparity for a newly identified minor histocompatibility antigen, HA-8, correlates with acute graft-versus-host disease after haematopoietic stem cell transplantation from an HLA-identical sibling. *Br J Haematol* 2003; **123**: 671–675.
- 7 den Haan JM, Meadows LM, Wang W, Pool J, Blokland E, Bishop TL *et al*. The minor histocompatibility antigen HA-1: a diallelic gene with a single amino acid polymorphism. *Science* 1998; **279**: 1054–1057.
- 8 Mommaas B, Kamp J, Drijfhout JW, Beekman N, Ossendorp F, Van Veelen P *et al*. Identification of a novel HLA-B60-restricted T cell epitope of the minor histocompatibility antigen HA-1 Locus. *J Immunol* 2002; **169**: 3131–3136.
- 9 Pierce RA, Field ED, Mutis T, Golovina TN, Von Kap-Herr C, Wilke M *et al*. The HA-2 minor histocompatibility antigen is derived from a diallelic gene encoding a novel human class I myosin protein. *J Immunol* 2001; **167**: 3223–3230.
- 10 Brickner AG, Warren EH, Caldwell JA, Akatsuka Y, Golovina TN, Zarling AL *et al*. The immunogenicity of a new human minor histocompatibility antigen results from differential antigen processing. *J Exp Med* 2001; **193**: 195–206.
- 11 Bunce M, O'Neill CM, Barnardo MC, Krausa P, Browning MJ, Morris PJ *et al*. Phototyping: comprehensive DNA typing for HLA-A, B, C, DRB1, DRB3, DRB4, DRB5 & DQB1 by PCR with 144 primer mixes utilizing sequence-specific primers (PCR-SSP). *Tissue Antigens* 1995; **46**: 355–367.
- 12 Murata M, Emi N, Hirabayashi N, Hamaguchi M, Goto S, Wakita A *et al*. No significant association between HA-1 incompatibility and incidence of acute graft-versus-host disease after HLA-identical sibling bone marrow transplantation in Japanese patients. *Int J Hematol* 2000; **72**: 371–375.
- 13 Pietz BC, Warden MB, DuChateau BK, Ellis TM. Multiplex genotyping of human minor histocompatibility antigens. *Hum Immunol* 2005; **66**: 1174–1182.
- 14 Arostegui JI, Gallardo D, Rodriguez-Luaces M, Querol S, Madrigal JA, Garcia-Lopez J *et al*. Genomic typing of minor histocompatibility antigen HA-1 by reference strand mediated conformation analysis (RSCA). *Tissue Antigens* 2000; **56**: 69–76.
- 15 Di Terlizzi S, Zino E, Mazzi B, Magnani C, Tresoldi C, Perna SK *et al*. Therapeutic and diagnostic applications of minor histocompatibility antigen HA-1 and HA-2 disparities in allogeneic hematopoietic stem cell transplantation: a survey of different populations. *Biol Blood Marrow Transplant* 2006; **12**: 95–101.
- 16 Marijt WA, Heemskerk MH, Kloosterboer FM, Goulmy E, Kester MG, van der Hoorn MA *et al*. Hematopoiesis-restricted minor histocompatibility antigens HA-1- or HA-2-specific T cells can induce complete remissions of relapsed leukemia. *Proc Natl Acad Sci USA* 2003; **100**: 2742–2747.
- 17 Spierings E, Goulmy E. Expanding the immunotherapeutic potential of minor histocompatibility antigens. *J Clin Invest* 2005; **115**: 3397–3400.
- 18 Gallardo D, Arostegui JI, Balas A, Torres A, Caballero D, Carreras E *et al*. Disparity for the minor histocompatibility antigen HA-1 is associated with an increased risk of acute graft-versus-host disease (GvHD) but it does not affect chronic GvHD incidence, disease-free survival or overall survival after allogeneic human leucocyte antigen-identical sibling donor transplantation. *Br J Haematol* 2001; **114**: 931–936.

- 19 Choi HB, Kim TG, Chung TJ, Han H. The distribution of HLA-A*02 subtype in Koreans. *Korean J Immunol* 1998; **20**: 31–37.
- 20 Del Guercio MF, Sidney J, Hermanson G, Perez C, Grey HM, Kubo RT *et al*. Binding of a peptide antigen to multiple HLA alleles allows definition of an A2-like supertype. *J Immunol* 1995; **154**: 685–693.
- 21 Nesci S, Buffi O, Iliescu A, Andreani M, Lucarelli G. Recipient mHag–HA1 disparity and aGVHD in thalassemic-transplanted patients. *Bone Marrow Transplant* 2003; **31**: 575–578.
- 22 Tseng LH, Lin MT, Hansen JA, Gooley T, Pei J, Smith AG *et al*. Correlation between disparity for the minor histocompatibility antigen HA-1 and the development of acute graft-versus-host disease after allogeneic marrow transplantation. *Blood* 1999; **94**: 2911–2914.
- 23 Rufer N, Wolpert E, Helg C, Tiercy JM, Gratwohl A, Chapuis B *et al*. HA-1 and the SMCY-derived peptide FIDSYICQV (H-Y) are immunodominant minor histocompatibility antigens after bone marrow transplantation. *Transplantation* 1998; **66**: 910–916.