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Donor Killer Immunoglobulin-Like Receptor Haplotype B/x Induces Severe Acute Graft-versus-Host Disease in the Presence of Human Leukocyte Antigen Mismatch in T Cell–Replete Hematopoietic Cell Transplantation

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Natural killer cells have been identified as a mediator of alloimmune reactions in allogeneic hematopoietic stem cell transplantation (HSCT). Killer immunoglobulin-like receptors (KIRs) are an important determinant of natural killer cell function. The relationship between KIR genotypes/haplotypes and clinical outcomes of allogeneic HSCT is complex and inconsistent among several reports. We assessed the clinical impact of KIR haplotype on T cell–replete allogeneic HSCTs performed in a single Japanese center for hematological malignancies (n = 106). A comparison of 2 groups, donor haplotypes A/A and B/x, revealed no significant differences in overall survival, relapse, and nonrelapse mortality. However, grade III to IV acute graft-versus-host disease (GVHD) occurred significantly more frequently in the KIR haplotype B/x group (A/A versus B/x: 4.9% versus 20.0%; $P = .02$). This was even more evident when HLA mismatch was present. The highest incidences of grade II to IV and grade III to IV acute GVHD were observed in patients who received allografts from HLA-mismatched donors with KIR haplotype B/x. These data highlight the importance of KIR genotyping in donor matching, especially when HLA mismatch allogeneic grafting is planned.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) has curative potential for patients with refractory or relapsed hematological malignancies. In addition to systemic radiotherapy and/or high-dose chemotherapy, graft-versus-leukemia (GVL) responses are beneficial for the control of intractable disease. While T cells play a major role in the GVL effect, natural killer (NK) cells have also been identified as potential mediators of GVL [1].

NK cells can recognize and kill transformed cells and virally infected cells without prior sensitization by using an array of cell surface receptors, including killer immunoglobulin-like receptors (KIRs), which bind to HLA class I molecules as a ligand and transduce inhibitory or activating signals [1]. After T cell–depleted unrelated HSCT, NK cells reconstitute in peripheral blood faster than T cells [2]. Ruggeri et al. were the first group to demonstrate the striking GVL response exerted by alloreactive NK cells, defined by "ligand-ligand" KIR mismatch model, after T cell–depleted HLA-haploidentical HSCT for acute myeloid leukemia (AML) [3]. The missing ligand model can define KIR-HLA mismatch in HLA-identical settings. Indeed, the beneficial effect of a missing KIR ligand was found in patients with AML and myelodysplastic syndrome after receiving ex vivo T cell–depleted allografts from HLA-identical siblings [4]. However, subsequent findings from other institutions worldwide have been inconsistent and controversial, probably because of the variety of factors that can affect transplantation outcomes, including stem cell source, conditioning intensity, HLA matching, usage of ex vivo or in vivo T cell depletion, or definition of KIR matching [5-8].

Recent studies have demonstrated the effect of KIR genotypes on the outcomes of HSCT. The KIR gene locus, located

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at chromosome 19, comprises 2 haplotypes, designated A and B [1]. The most common haplotype, A, contains *KIR2DL1*, *2DL3*, *2DL4*, *3DL1*, *3DL2*, and a single activating receptor *KIR2DS4*. The group B haplotypes essentially consist of all other KIR combinations, but importantly, it contains more activating receptors. Cooley et al. reported a 30% improvement in the relative risk of relapse-free survival in patients with AML who received allografts from unrelated KIR B/x haplotype donors [9]. However, similar to the effects of KIR ligand mismatch, conflicting results have been reported with respect to the effect of KIR genotypes/haplotypes on the clinical outcomes of various types of allogeneic HSCT [5,10-13].

In this study, we retrospectively analyzed the impact of KIR ligand status and KIR haplotypes on the clinical outcomes of allogeneic HSCT in Japanese patients and donors.

MATERIALS AND METHODS

Patients and Donors

From January 1989 to September 2011, a total of 304 allogeneic HSCTs were performed at Niigata University Medical and Dental Hospital. All patients and donors were Japanese. DNA samples for KIR typing were available from 152 donors. Of these, HLA haploidentical HSCTs (n = 7), HSCT with administration of antithymocyte globulin (ATG; n = 1), HSCTs for nonhematological malignancies (n = 6), and cord blood transplantation (n = 32) were excluded. The remaining 106 T cell–replete HSCTs, without administration of ATG, for hematological malignancies were enrolled. The donor sources contained HLA-matched sibling donors, mismatched family donors, and unrelated donors.

Donor DNA samples were prepared for short tandem repeat analysis to enable recipient-donor identification, and were cryopreserved for future clinical demands. The ethical committee of Niigata University School of Medicine approved the study protocol. The data and sample committee of the Japan Marrow Donor Program (JMDP) also approved the protocol.

Pairs of family donors and recipients were prospectively assessed for HLA compatibility, mainly by serologic typing. Pairs of unrelated donors and recipients were prospectively assessed for HLA compatibility by serologic typing of HLA-A, -B, and -DRB1 until 2006 and by DNA typing of HLA-A, -B, -C, and -DRB1 from 2007 onward. HLA allele data (HLA-A, -B, -C, -DRB1, and DQB1) of 41 donor/recipient pairs (out of 53 unrelated bone marrow transplantation pairs), which were retrospectively retyped by the JMDP, were provided by the data and sample committee of the JMDP in 2015. In 7 mismatched family and 6 unrelated pairs, retrospective HLA allele retyping could not be performed because of unavailability of recipient DNA.

Acute graft-versus-host disease (GVHD) was diagnosed and graded according to the standard criteria [14]. All patients received GVHD prophylaxis comprising cyclosporine or tacrolimus. Ex vivo T cell depletion was not performed.

KIR Genotyping and Haplotype Assignment

DNA samples from the donors were tested for the presence or absence of 16 KIR genes (listed in Figure S1) by the PCR-rSSO method (KIR SSO Genotyping Test; OneLamda, Canoga Park, CA). Donors were assigned the A/A or B/x genotype as defined previously [9]. Genotypes for the centromeric (Cen) and telomeric (Tel) parts of the KIR locus were assigned as defined previously [15]. KIR B-content score was calculated according to the definition reported elsewhere [15].

KIR ligand mismatch (the ligand-ligand model) in the graft-versus-host direction was determined according to the algorithm proposed by Ruggeri et al. [3] in all recipients who had complete data sets for HLA alleles. KIR ligand mismatch for *KIR3DL2* was not considered. KIR mismatch in the graft-versus-host direction was determined by missing KIR ligand model according to the algorithm reported by Hsu et al. [4]. Briefly, *missing KIR ligand* was defined if 1 or more recipient HLA ligands for the identified donor inhibitory KIRs were absent.

Statistical Analysis

Baseline categorical variables were compared between KIR haplotype groups using Fisher's exact test, whereas continuous variables were compared by the Mann-Whitney U-test. Four outcomes were analyzed between KIR haplotype groups: overall survival (OS), relapse, nonrelapse mortality (NRM), and acute GVHD. OS was estimated by the Kaplan-Meier method and analyzed by the log-rank test. The probabilities of relapse, NRM, and acute GVHD were calculated as the cumulative incidence to enable adjustment for competing risks [16]. For relapse, NRM was the competing event; for NRM, relapse was the competing event; and for GVHD, death without GVHD was the competing event. The cumulative incidences of relapse, NRM, and acute GVHD were compared using Gray's test. Fine and Gray's multivariate method was used to evaluate risk factors for GVHD. Variables that were significant on univariate analysis at $P < .10$ were included in multivariate analysis and a stepwise backward elimination was used to eliminate all variables with $P > .05$. A value of $P < .05$ was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [17].

Table 1
Patient Characteristics

Characteristic	Donor KIR Haplotype		*P*
	Haplotype A/A, n = 61 (57.5%)	Haplotype B/x, n = 45 (42.5%)	
Age, median (range), yr	38 (17-62)	35 (10-61)	.26
Follow-up, median (range), d	2950 (557-8790)	3468 (515-6586)	.74
Patient sex			
Male	31 (50.8)	24 (53.3)	.85
Female	30 (49.2)	21 (46.7)	
Graft type			
Related BMT	20 (32.8)	13 (28.9)	.76
Related PBSCT	10 (16.4)	10 (22.2)	
Unrelated BMT	31 (50.8)	22 (48.9)	
HLA matching*			
Matched sibling	21 (34.4)	15 (33.3)	.91
Unrelated 10/10 allele matched	14 (23.0)	8 (17.8)	
Less than 10/10	19 (31.1)	16 (35.6)	
Unknown	7 (11.5)	6 (13.3)	
KIR ligand mismatch (GVH direction)			
Matched	53 (86.9)	38 (84.4)	.21
Mismatched	2 (3.3)	5 (11.1)	
Unknown	6 (9.8)	2 (4.4)	
Missing KIR ligand			
0 Missing ligand	7 (11.5)	6 (13.3)	.44
1-2 Missing ligand	38 (62.3)	32 (71.1)	
Unknown	16 (26.2)	7 (15.6)	
Diagnosis			
AML	26 (42.6)	18 (40.0)	.67
ALL	17 (27.9)	11 (24.4)	
CML	9 (14.8)	5 (11.1)	
MDS	5 (8.2)	4 (8.9)	
NHL	4 (6.6)	7 (15.6)	
Disease status			
CR 1, RA	31 (50.8)	22 (48.9)	.93
CR 2, AP	12 (19.7)	8 (17.8)	
CR 3, non CR, RAEB	18 (29.5)	15 (33.3)	
Conditioning regimen			
Myeloablative	52 (85.2)	38 (84.4)	1.00
Reduced intensity	9 (14.8)	7 (15.6)	
GVHD prophylaxis			
With cyclosporine	51 (83.6)	34 (75.6)	.33
With tacrolimus	10 (16.4)	11 (24.4)	

Data presented are n (%) unless otherwise indicated.
BMT indicates bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; GVH, graft-versus-host; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; CR, complete remission; RA, refractory anemia; AP, accelerated phase; RAEB, refractory anemia with excess blasts.
* The category "less than 10/10" includes unrelated donor/recipient pairs with HLA compatibility equal or less than 9/10 and mismatched family pairs. "Unknown" includes donor-recipient pairs with HLA-match by serology (HLA 6/6 match or 8/8 match) but without HLA allele data.

RESULTS

Patient Characteristics

The patient characteristics are presented in Table 1. Among the 106 donors, 61 (57.5%) were KIR haplotype A/A and 45 (42.5%) were KIR haplotype B/x. The frequencies of KIR genotype/haplotype were similar to those reported in previous studies in Japanese populations [18] (Figure S1).

KIR ligand mismatches (the ligand-ligand model) in the graft-versus-host direction were present in only 7 (7.1%) of 98 assessable pairs with 2 haplotype A/A and 5 haplotype B/x, reflecting the low frequency of C2-allele within Japanese population [6]. Thus, the impact of the KIR ligand mismatch model on clinical outcomes could not be assessed in this cohort. In contrast, at least 1 missing KIR ligand was present in 70 of 83 assessable pairs, with 38 haplotype A/A and 32 haplotype B/x.

OS, Relapse and NRM

Donor KIR haplotypes had no significant effect on the 5-year OS (A/A: 64.6%; 95% confidence interval [CI], 50.9 to 75.4 versus B/x: 52.5%; 95% CI, 36.8 to 66.0; $P = .32$), the 5-year cumulative incidence of relapse (A/A: 30.3%; 95% CI, 19.0 to 42.3 versus B/x: 33.3%; 95% CI, 20.0 to 47.3; $P = .64$), and the 5-year cumulative incidence of NRM (A/A: 13.1%; 95% CI, 6.1 to 22.9 versus B/x: 15.6%; 95% CI, 6.7 to 27.7; $P = .59$). Because the cohort included several types of hematological malignancies, while graft sources were variable, subpopulation analysis was abandoned.

Effect of KIR Haplotypes on Acute GVHD

There were no significant differences between donor KIR haplotype A/A and B/x in the cumulative incidences of any grade of acute GVHD (A/A: 54.1%; 95% CI, 39.7 to 65.0 versus B/x: 57.8%; 95% CI, 40.6 to 70.0; $P = .97$) (Figure 1A). In contrast, there was a trend toward a higher cumulative incidence of grade II to IV acute GVHD in patients receiving grafts from donors with KIR haplotype B/x than those receiving grafts from donors with KIR haplotype A/A (A/A: 16.4%; 95% CI, 8.4 to 26.8 versus B/x: 33.3%; 95% CI, 20.0 to 47.2; $P = .051$) (Figure 1B). Furthermore, the risk of grade III to IV acute GVHD was significantly increased in patients receiving grafts from KIR haplotype B/x donors (A/A: 4.9%; 95% CI, 1.3 to 12.5 versus B/x: 20.0%; 95% CI, 9.8 to 32.8; $P = .02$) (Figure 1C). We analyzed effect of centromeric (Cen A/A, Cen A/B, Cen B/B) and telomeric (Tel A/A, Tel A/B, Tel B/B) KIR genotypes and KIR B-content score on the incidence of acute GVHD but observed no significant differences (data not shown).

Effect of KIR Haplotypes and Missing KIR Ligand Status on Acute GVHD

As a general concept that governs human NK cell functions, NK cells become tolerant to cells expressing self-HLA class I molecules when signals from inhibitory KIRs surpass those from activating KIRs. Therefore, the cumulative incidence of grade II or higher acute GVHD was analyzed by missing KIR ligand status (inhibitory signal status) in addition to KIR haplotypes (activating signal status). Because of the small sample size, groups without missing ligand status (with KIR haplotypes A/A or B/x) were pooled. The cumulative incidence of grade II to IV acute GVHD was significantly higher in patients with at least 1 missing ligand who received allografts from donors of KIR haplotype B/x compared with KIR haplotype A/A, and in patients without missing ligands (no missing ligand: 15.4%; 95% CI, 2.2 to 39.8 versus 1 missing ligand and A/A: 18.4%; 95% CI, 8.0 to 32.2 versus 1 missing ligand and B/x: 43.8%; 95% CI, 26.1 to 60.1; $P = .042$) (Figure 1D). Similarly, the cumulative incidence of grade III to IV acute GVHD was highest in patients with at least 1 missing ligand who received allografts from KIR haplotype B/x donors (no missing ligand: 7.7%; 95% CI, .4 to 30.3 versus 1 missing ligand and A/A: 5.3%; 95% CI, .9 to 15.7 versus 1 missing ligand and B/x: 25.0%; 95% CI, 11.6 to 41.0; $P = .047$) (Figure 1E).

Effect of KIR Haplotypes and HLA Matching on Acute GVHD

It has been reported that the degree of T cell alloreactivity influences the development and function of NK cells after engraftment [2,19]. Therefore, the cumulative incidence of acute GVHD was analyzed by HLA matching in addition to KIR haplotypes. HLA-matched sibling donors and 10 of 10 HLA allele–matched unrelated donors were defined as the *HLA-match group*, whereas donors with at least 1 HLA allele mismatch were defined as the *HLA-mismatch group*. Donors with only serologically defined HLA data were excluded. The highest cumulative incidence of grade II to IV acute GVHD was observed in patients who received allografts from HLA-mismatched donors with KIR haplotype B/x among the 4 groups (HLA match and KIR A/A: 14.3%; 95% CI, 5.1 to 28.0 versus HLA match and KIR B/x: 21.7%; 95% CI, 7.7 to 40.4 versus HLA mismatch and KIR A/A: 21.1%; 95% CI, 6.3 to 41.7 versus HLA mismatch and KIR B/x: 56.2%; 95% CI, 28.0 to 77.1; $P = .014$) (Figure 1F). The same trend was found for grade III to IV acute GVHD, and the highest incidence of grade III to IV acute GVHD occurred in patients who received allografts from HLA-mismatched donors with KIR haplotype B/x (HLA match and KIR A/A: 5.7%; 95% CI, 1.0 to 16.9 versus HLA match and KIR B/x: 8.7%; 95% CI, 1.4 to 24.6 versus HLA mismatch and KIR A/A: 5.3%; 95% CI, .3 to 22.0 versus HLA mismatch and KIR B/x: 37.5%; 95% CI, 14.6 to 60.7; $P = .006$) (Figure 1G). Both comparisons among the 4 groups were statistically different.

Univariate and Multivariate Analysis of Acute GVHD

Univariate analysis was performed for variables, including KIR haplotypes, donor types, HLA matching, KIR ligand mismatch, missing KIR ligand, diagnosis, stage, conditioning regimen, and GVHD prophylaxis, to identify the impact on acute GVHD (Table 2). For grade II to IV acute GVHD, donor KIR haplotypes and HLA matching were identified as significant factors ($P < .10$). Multivariate analysis was conducted with stepwise backward elimination, including the 2 factors identified in univariate analysis, and HLA-mismatched donor was the only significant risk factor (hazard ratio: 2.54; 95% CI, 1.13 to 5.73; $P = .02$). For grade III to IV acute GVHD, donor KIR haplotypes, HLA matching, and GVHD prophylaxis were identified as significant factors in univariate analysis. However, because of the limited sample size, we could not perform multivariate analysis.

DISCUSSION

To investigate the impact of donor KIR haplotypes on clinical outcomes after allogeneic HSCT, we retrospectively analyzed data from patients with hematological malignancies who received T cell–replete HSCT (with neither ex vivo nor in vivo T cell depletion) at a single Japanese center and found that incidence of grade III to IV acute GVHD was significantly higher in recipients receiving allografts from KIR haplotype B/x donors than from KIR haplotype A/A donors. Although GVHD is believed to be a T cell–mediated disease, previous study has shown that NK cell interferon-gamma production could increase acute GVHD [19]. In our cohort, the incidences of grade II to IV and grade III to IV acute GVHD were significantly higher in allografts from KIR haplotype B/x donors with missing KIR ligand(s) than from KIR haplotype A/A donors with missing KIR ligand(s) or donors without

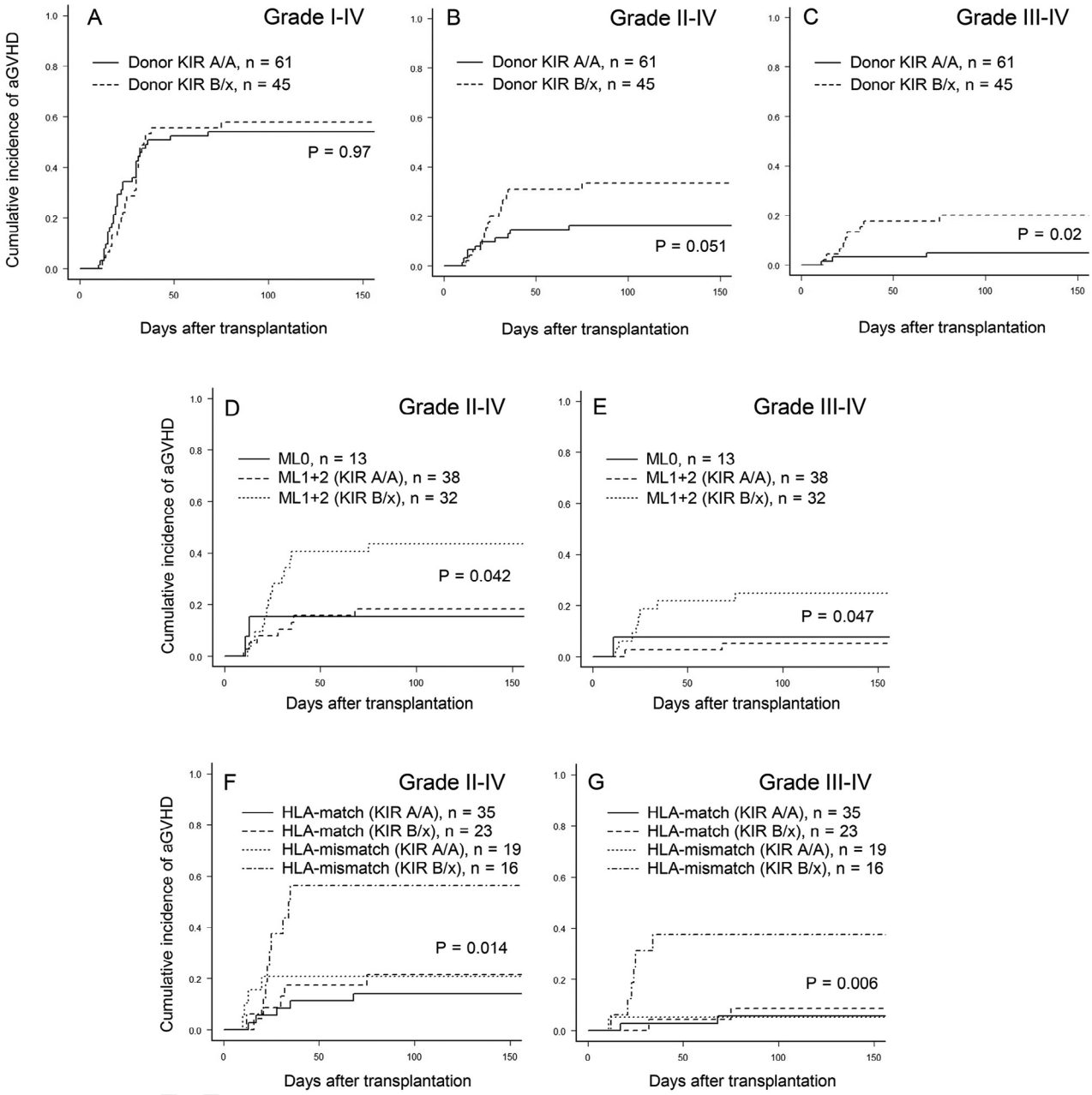

Figure 1. The association of donor KIR haplotypes on acute GVHD. The cumulative incidence of grade I to IV (A), grade II to IV (B), grade III and IV (C) acute GVHD according to KIR haplotypes are shown. The risk of grade III and IV acute GVHD was significantly higher in patients receiving allografts from KIR haplotype B/x donors. The cumulative incidences of grade II to IV (D) and grade III and IV (E) acute GVHD were higher in recipients with KIR haplotype B/x donors with missing KIR ligand(s) than in those with KIR haplotype A/A donors with missing KIR ligand(s), or in those without missing KIR ligand. When assessing HLA matching, the cumulative incidences of grade II to IV (F) and grade III and IV (G) acute GVHD were highest in recipients with donors harboring HLA mismatch and KIR haplotype B/x. ML0 represents donors without missing KIR ligand. ML1+2 represents donors with at least 1 missing KIR ligands.

missing KIR ligand. This may indicate that the combination of low levels of inhibitory KIR signals and high levels of activating KIR signals can enhance NK cell function, consequently stimulating pre-existing allogeneic T cell response and increasing the incidence of acute GVHD [20]. It is well established that HLA matching between donors and recipients is the key factor that affects clinical outcomes after allogeneic HSCT [21]. Indeed, in multivariate analysis of our cohort, only HLA mismatch was identified as an independent risk factor for grade II to IV acute GVHD. When assessing KIR haplotypes together with HLA matching, the incidence of acute GVHD was increased in allografts from donors with HLA-mismatch and KIR haplotype B/x, not from those with HLA-mismatch and KIR haplotype A/A or HLA-matched donors. In other words, absence of activating KIRs other than *KIR2DS4* protected recipients receiving HLA-mismatched, KIR haplotype A/A donors from developing higher grade acute GVHD.

There have been conflicting reports on the association of activating KIR genotypes/haplotypes with clinical outcomes, including GVHD. Bishara et al. reported that the presence of activating KIRs in the donor accelerated the se-

Table 2
Univariate Analysis of Grade II to IV Acute GVHD

Variable	n	Univariate Analysis		Multivariate Analysis	
		Cumulative Incidence (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
KIR haplotype					
Haplotype A/A	61	16.4 (8.4-26.8)	.051		
Haplotype B/x	45	33.3 (20.0-47.2)			
Donor type					
Related donor	53	22.6 (12.4-34.7)	.80		
Unrelated donor	53	24.5 (13.9-36.8)			
HLA matching					
10/10 Allele matched	58	17.2 (8.8-28.0)	.02	1.00	.02
Less than 10/10	35	37.1 (21.4-53.0)		2.54 (1.13-5.73)	
KIR ligand mismatch					
Matched	91	23.1 (15.0-32.2)	.78		
Mismatched	7	28.6 (3.1-63.6)			
Missing KIR ligand					
0 Missing ligand	13	15.4 (2.2-39.8)	.35		
1-2 Missing ligands	70	30.0 (19.7-41.0)			
Diagnosis*					
Myeloid malignancy	67	22.4 (13.2-33.0)	.70		
Lymphoid malignancy	39	25.6 (13.2-40.1)			
Stage†					
Low risk	53	18.9 (9.6-30.5)	.29		
High risk	53	28.3 (16.9-40.9)			
Conditioning regimen					
Myeloablative	90	23.3 (15.2-32.5)	.97		
Reduced intensity	16	25.0 (7.3-48.0)			
GVHD prophylaxis					
With cyclosporine	85	21.2 (13.2-30.4)	.21		
With tacrolimus	21	33.3 (14.4-53.7)			

* Myeloid malignancy includes AML, CML, and MDS. Lymphoid malignancy includes ALL and NHL.
† Low risk includes first complete remission and refractory anemia. High risk includes second CR, third CR, non CR, AP, and RAEB.

verity of acute GVHD [5]. Yabe et al. used the Japanese database (JMDP) to analyze cases with uniform GVHD prophylaxis after myeloablative conditioning and T cell–replete unrelated bone marrow transplantation, and showed that acute GVHD were more frequent in donors with *KIR2DS2*, only when donor/recipient pairs were KIR-ligand mismatched [6]. These observations are in concordance with our findings. In contrast, in the largest study on the association between KIR haplotypes and outcomes in T cell–replete unrelated HSCT, there was no difference in the incidence of grade II to IV acute GVHD between donors with KIR haplotype A/A or B/x [9]. In a Chinese cohort comprising HLA-identical sibling HSCTs, multivariate analysis did not reveal differences according to donor KIR haplotype (A/A or B/x) for acute GVHD [13]. On the contrary, Littera et al. reported that KIR haplotype A/A donors conferred a greater risk of developing grade II to IV acute GVHD than KIR haplotype B/x donors [11]. In this cohort, the use of in vivo T cell depletion of unrelated allografts with ATG and a high level of HLA matching (83.3% were 10/10 HLA matched) may have produced an environment with deeply suppressed T cell alloreactivity, thereby enhancing NK cell alloreactivity. In unrelated HSCTs in which 62% were 10/10 HLA matched and 19% received T cell depletion, the presence of *KIR3DS1* in the donor was associated with a reduced incidence of grade II to IV acute GVHD [12]. Taken together, these findings suggest that the magnitude of T cell alloreactivity (HLA matching) may affect the role of donor KIR genotypes and haplotypes in the incidence and severity of acute GVHD.

In our study, donors and recipients were all Japanese. Differences exist in the risk for acute GVHD by ethnicity [22], and KIR haplotype distribution and HLA-C allele frequencies also differ by ethnicity. In a Japanese cohort, the frequency of C1/C1, C1/C2, and C2/C2 alleles were 85.8%, 13.4%, and .81%, respectively [6]. Chinese populations have a different pattern of HLA-C allele distribution: C1/C1 in 63.0%, C1/C2 in 26.0%, and C2/C2 in 11.0% [13]. In contrast, an Austrian cohort comprised C1/C1 in 40%, C1/C2 in 47%, and C2/C2 in 13% [7]. Moreover, frequency of KIR haplotype B/x in Japanese populations is lower than in Caucasian populations [18]. In Japanese populations, the distribution of KIR haplotypes is 56% for A/A and 44% for B/x, whereas in Western countries, KIR haplotype B/x is predominant, occurring in approximately 70% of the population [9,18]. Therefore, it is relevant to analyze the association between KIR and GVHD in different ethnic groups.

In conclusion, our data shows that donor KIR haplotype B/x may affect the incidence of acute GVHD in T cell–replete HSCTs, especially when HLA mismatch is present, in Japanese patients. Therefore, it is important to determine the KIR genotype/haplotype of potential allograft donors to identify those at risk of GVHD. In allogeneic HSCT from donors with HLA mismatch and KIR haplotype B/x, inclusion of ATG in preconditioning may be recommended. KIR typing before donor matching is desired in the future with marrow and cord blood banking systems. Although the present findings are of general interest, results may differ depending on the degree of T cell alloreactivity, and ethnic differences. Because the relationship between KIR haplotypes and clinical outcomes of allo-HSCT is complex, and this study cohort was too small to draw conclusive results, further studies are needed to clarify the role of donor NK cells in allogeneic HSCT.

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2016.12.638.

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