Supplemental data

HLA-DQ Heterodimers in Hematopoietic-Cell Transplantation

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Supplemental Table 1. Demographics of the Study Population

Characteristic	**HLA-A,-B,-C,-DRB1,-DQA1,-DQB1-matched *n* = 5,164**	**One HLA-DQB1 allele mismatch (HLA-A,-B,-C,-DRB1-matched) *n* = 520**
Age, average yrs (range)		
Patient	39.0 (0.5 – 76.5)	35.2 (0.3 – 72.7)
Donor	35.1 (18.3 – 61.2)	36.3 (18.7 – 61.2)
Year of transplantation – no. (%)		
1988-1990	104	7
1991-1995	573	55
1996-2000	1,083	117
2001-2005	1,986	207
2006-2010	1,123	98
2011-2016	295	36
Patient sex – no. (%)		
Female	2,200	216
Male	2,963	304
Not specified	1	0
Donor sex – no. (%)		
Female	1,697	205
Male	3,417	313
Not specified	50	2
Disease – no. (%)		
ALL	865	78
AML	1,734	146
CML	1,003	80
MDS	892	80
Lymphoma*	423	45
Myeloma	6	4
Other malignant blood disorders†	29	32
Other malignant non-blood disorders‡	3	1
Non-malignant§	208	54
Not specified	1	0
Disease status¶ - no. (%)		
Early	2,015	176

Intermediate	1,097	76
Late	1,180	95
Other	872	173
Patient-Donor CMV serological status – no. (%)		
Negative/Negative	1,717	139
Negative/Positive	542	58
Positive/Negative	1,659	172
Positive/Positive	841	100
Not specified	405	51
Transplant type – no. (%)		
Myeloablative	4,042	380
Nonmyeloablative/ reduced intensity	950	110
Not specified	172	30
Source of cells – no. (%)		
Bone marrow	2,865	308
Peripheral blood stem cells	2,274	210
Bone marrow and peripheral blood stem cells	24	1
Not specified	1	1
Total body irradiation – no. (%)		
Yes	2,935	274
No	2,213	236
Not specified	16	10
GVHD prophylaxis – no. (%)		
Calcineurin-containing	4,579	464
Other[ll]	576	56
Not specified	9	0
T-cell depletion – no. (%)		
Yes	1,615	192
No	3,517	324
Not specified	32	4
DPB1 match status – no. (%)		

Matched	720	42
One mismatch	2,517	233
Two mismatches	1,306	169
No data	621	76
HLA-DQA1 matching in GVH vector		
Matched	5,164	433
Number of unique HLA-DQ patient molecules		
1	532	0
2	3,208	324
4	1,424	196
Patient HLA-DQ genotype		
Group 1, Group 1	1,691	182
Group 1, Group 2	2,573	271
Group 2, Group 2	900	67
Patient genotype and mismatched molecule		
Group 1, Group 1 (Group 1 mismatch)	0	182
Group 1, Group 2 (Group 1 mismatch)	0	148
Group 1, Group 2 (Group 2 mismatch)	0	123
Group 2, Group 2 (Group 2 mismatch)	0	67
Matched	5,164	0
Donor HLA-DQ genotype		
Group 1, Group 1	1,691	193
Group 1, Group 2	2,573	263
Group 2, Group 2	900	64

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome.

Variables are defined according to established definitions.[1]

* Hodgkin lymphoma, non-Hodgkin lymphoma

† Other malignant blood disorders: other acute or chronic leukemia not otherwise specified.

‡ Other malignant non-blood disorders: breast cancer, renal carcinoma, rhabdomyosarcoma

§ Nonmalignant disorders: histiocytic disorders; inherited abnormality of erythrocyte differentiation or function; inherited disorder of metabolism; severe aplastic anemia; severe combined immunodeficiency and other immune system disorders, unspecified.

¶ Disease Status: early (first complete remission in AML or ALL; first chronic phase CML; refractory anemia; refractory anemia with ringed sideroblasts; refractory cytopenia with multilineage dysplasia; myelodysplastic syndrome); intermediate (second or higher complete remission in AML or ALL; second or higher chronic phase or accelerated phase in CML); late (primary induction failure; first or higher relapse in AML or ALL; blast phase CML; CMML; refractory anemia with excess blasts [RAEB]; RAEB in transformation (t); RAEB-1; RAEB-2; greater than 5% blasts in myelodysplastic syndrome); other (un-named myelodysplasia, myeloproliferative disorder).

‖ Other GVHD prophylaxis regimens containing anti-lymphocyte globulin/serum, Campath, methotrexate, corticosteroids, sirolimus, mycophenolate mofetil. A total of 10 recipients received post-transplant cyclophosphamide.

Supplemental Table 2. IHWG Participants

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Supplemental Table 3. Patient and Donor Mismatches

Among 324 patients with one mismatched HLA-DQ molecule, the cis-encoded allele genotype is described by the group genotype G1G1, G1G2 and G2G2. When the mismatched HLA-DQ molecule is considered, a total of eight patient/donor genotype and mismatch combinations are possible. G1G2 patients may be mismatched for either the G1 or the G2 molecule (the mismatched molecule is underlined).

Patient genotype and mismatched molecule	**Donor genotype and mismatched molecule**				**Total**
	G1G1	**G1G2**	**G1G2**	**G2G2**	
G1G1	30	-	2	-	32
G1G2	-	135	-	13	148
G1G2	23	-	100	-	123
G2G2	-	3	-	18	21
Total	53	138	102	31	324

-, not applicable. Transplant pairs had only a single HLA-DQB1 allele mismatch at transplant.

Supplemental Table 4. Models for HLA-matched Transplantation

Model	**Population**	**Endpoint**	**Group**	**Number**	**Hazard ratio (95% CI; *P* value)**
Total number of HLA-DQ molecules in HLA-matched transplants	HLA-matched transplants *n* = 5,164	Relapse	One	495	1.0
			Two	3,036	1.23 (1.04 – 1.46; 0.02)
			Four	1,348	1.16 (0.96 – 1.39; 0.12)
		Disease-free survival	One	532	1.0
			Two	3,200	1.08 (0.97 – 1.21; 0.16)
			Four	1,419	1.08 (0.96 – 1.22; 0.21)
		Mortality	One	532	1.0
			Two	3,208	1.05 (0.94 – 1.18; 0.38)
			Four	1,424	1.06 (0.94 – 1.20; 0.32)
		II-IV Acute GVHD	One	522	1.0
			Two	3,160	0.96 (0.80 – 1.16; 0.68)
			Four	1,390	0.96 (0.78 – 1.18; 0.72)
		III-IV Acute GVHD	One	508	1.0
			Two	3,093	0.88 (0.70 – 1.11; 0.29)
			Four	1,359	0.92 (0.71 – 1.19; 0.52)
		Chronic GVHD	One	521	1.0
			Two	3,140	0.85 (0.75 – 0.97; 0.02)
			Four	1,379	0.89 (0.77 – 1.02; 0.10)

Genotype in HLA-matched transplants	HLA-matched transplants *n* = 5,164	Mortality	G1G1	1,691	1.0
			G1G2	2,573	1.06 (0.98 – 1.14; 0.16)
			G2G2	900	1.07 (0.97 – 1.18; 0.19)
		II-IV Acute GVHD	G1G1	1,657	1.0
			G1G2	2,536	0.95 (0.84 – 1.08; 0.43)
			G2G2	879	0.92 (0.78 – 1.09; 0.33)
		III-IV Acute GVHD	G1G1	1,613	1.0
			G1G2	2,484	0.95 (0.81 – 1.12; 0.54)
			G2G2	863	1.13 (0.92 – 1.39; 0.24)
		Chronic GVHD	G1G1	1,649	1.0
			G1G2	2,513	0.93 (0.85 – 1.02; 0.12)
			G2G2	878	1.00 (0.89 – 1.12; 0.96)

Supplemental Table 5. HLA-DR15 and G2 in HLA-matched Transplantation

Among HLA-A,-B,-C,-DRB1,-DQA1,-DQB1-matched unrelated donor/patient pairs, the hazard ratios of relapse and disease-free survival are shown according to the HLA-DQ genotype (G1G1, G1G2, G2G2) and presence of any number of DR15 (one or two) or absence of DR15. No patient/donor pair with the G1G1 genotype was DR15-positive. The effect of G2 on relapse is observed in DR15-negative patients in whom G1G2 genotype is associated with higher risk of relapse compared to G1G1 genotype. Further evidence of a lack of a DR15 effect on relapse is observed in comparisons among G1G2 patients with and without DR15 (†) and among G2G2 patients with and without DR15 (‡). A similar lack of a DR15 effect is observed for disease-free survival (§, ¶). Interaction P values are 0.92 for relapse and 0.39 for disease-free survival.

Clinical endpoint	**Number**	**HLA-DQ genotype and presence of HLA-DR15**	**Hazard ratio (95% CI; *P* value)***
Relapse	1,597	G1G1 without DR15	1.0
	1,429	G1G2 without DR15†	1.20 (1.06 – 1.36; 0.003)
	1,005	G1G2 with any DR15†	1.22 (1.07 – 1.40; 0.004)
	283	G2G2 without DR15‡	1.19 (0.96 – 1.47; 0.11)
	565	G2G2 with any DR15‡	1.23 (1.05 – 1.44; 0.01)
Disease-free survival	1,688	G1G1 without DR15	1.0
	1,491	G1G2 without DR15§	1.04 (0.96 – 1.14; 0.32)
	1,075	G1G2 with any DR15§	1.12 (1.03 – 1.23; 0.01)
	309	G2G2 without DR15¶	1.11 (0.96 – 1.28; 0.15)
	588	G2G2 with any DR15¶	1.10 (0.99 – 1.23; 0.08)

*Models adjusted for the transplant conditioning regimen, diagnosis, CMV serostatus, patient age, donor age, stem cell source, donor sex, patient sex, use of total body radiation, use of T-cell depletion, presence of DPB1 mismatching.

† Compared to G1G2 without DR15, G1G2 with any DR15 had a hazard ratio of relapse of 1.02 (1.22 divided by 1.20).

‡ Compared to G2G2 without DR15, G2G2 with any DR15 had a hazard ratio of relapse of 1.03 (1.23 divided by 1.19).

§ Compared to G1G2 without DR15, G1G2 with any DR15 had a hazard ratio of disease-free survival of 1.08 (1.12 divided by 1.04).

¶ Compared to G2G2 without DR15, G2G2 with any DR15 had a hazard ratio of disease-free survival of 0.99 (1.10 divided by 1.11).

Supplemental Table 6. Models for HLA-DQ-mismatched Transplantation

The mismatched molecule is underlined.

Model		**Population**	**Endpoint**	**Group**	**Number**	**Hazard ratio (95% CI; *P* value)**
A	Number of patient mismatches	HLA-DQ-mismatched patients *n* = 520	Relapse	One mismatch	266	1.0
				Two mismatches	124	1.92 (0.94 – 3.91; 0.07)
				Three mismatches	34	1.89 (0.66 – 5.40; 0.23)
			Disease-free survival	One mismatch	316	1.0
				Two mismatches	147	1.46 (0.96 – 2.24; 0.08)
				Three mismatches	40	1.18 (0.61 – 2.30; 0.62)
			Mortality	One mismatch	324	1.0
				Two mismatches	155	1.22 (0.79 – 1.86; 0.37)

				Three mismatches	41	1.12 (0.56 – 2.21; 0.75)
			II-IV Acute GVHD	One mismatch	306	1.0
				Two mismatches	147	0.80 (0.41 – 1.55; 0.50)
				Three mismatches	41	2.54 (0.84 – 7.69; 0.10)
			Chronic GVHD	One mismatch	305	1.0
				Two mismatches	145	1.03 (0.64 – 1.66; 0.89)
				Three mismatches	41	1.67 (0.79 – 3.52; 0.18)
B	Number of patient G1 mismatches	HLA-DQ-mismatched patients *n* = 520	Relapse	Zero G1 mismatch	155	1.0
				One G1 mismatch	145	0.79 (0.53 – 1.20; 0.27)
				Two G1 mismatches	105	0.74 (0.46 – 1.18; 0.20)
				Three G1 mismatches	19	1.20 (0.47 – 3.05; 0.70)
			Disease-free survival	Zero G1 mismatch	184	1.0
				One G1 mismatch	174	0.80 (0.61 – 1.04; 0.09)
				Two G1 mismatches	123	0.80 (0.60 – 1.09; 0.16)

				Three G1 mismatches	22	0.78 (0.40 – 1.51; 0.46)
			Mortality	Zero G1 mismatch	190	1.0
				One G1 mismatch	180	0.87 (0.67 – 1.14; 0.31)
				Two G1 mismatches	128	0.85 (0.63 – 1.16; 0.31)
				Three G1 mismatches	22	0.68 (0.33 – 1.39; 0.29)
			II-IV Acute GVHD	Zero G1 mismatch	184	1.0
				One G1 mismatch	166	1.13 (0.71 – 1.79; 0.61)
				Two G1 mismatches	122	0.87 (0.53 – 1.45; 0.60)
				Three G1 mismatches	22	1.55 (0.53 – 4.57; 0.42)
C	Number of patient G2 mismatches	HLA-DQ-mismatched patients *n* = 520	Relapse	Zero G2 mismatch	269	1.0
				One G2 mismatch	121	1.25 (0.86 – 1.82; 0.25)
				Two G2 mismatches	19	1.60 (0.72 – 3.59; 0.25)
				Three G2 mismatches	15	0.58 (0.17 – 2.00; 0.39)
			Disease-free Survival	Zero G2 mismatch	319	1.0
				One G2 mismatch	142	1.20 (0.93 – 1.54; 0.16)
				Two G2 mismatches	24	1.73 (1.04 – 2.86; 0.03)

				Three G2 mismatches	18	1.15 (0.59 – 2.24; 0.68)
			Mortality	Zero G2 mismatch	330	1.0
				One G2 mismatch	144	1.17 (0.90 – 1.51; 0.25)
				Two G2 mismatches	27	1.22 (0.74 – 2.03; 0.44)
				Three G2 mismatches	19	1.26 (0.64 – 2.47; 0.50)
			II-IV Acute GVHD	Zero G2 mismatch	310	1.0
				One G2 mismatch	140	0.90 (0.58 – 1.39; 0.63)
				Two G2 mismatches	25	0.75 (0.31 – 1.81; 0.52)
				Three G2 mismatches	19	2.67 (0.76 – 9.31; 0.12)
D	Patient genotype	One HLA-DQ-mismatch *n* = 324	Mortality	G1G1	32	1.0
				G1G2	271	1.44 (0.88 – 2.37; 0.15)
				G2G2	21	1.41 (0.68 – 2.90; 0.36)
			II-IV Acute GVHD	G1G1	31	1.0
				G1G2	254	1.16 (0.53 – 2.52; 0.72)
				G2G2	21	1.13 (0.35 – 3.65; 0.84)
			Chronic GVHD	G1G1	32	1.0

				G1G2	252	0.96 (0.55 – 1.67; 0.89)
				G2G2	21	1.00 (0.42 – 2.37; 1.0)
E	Patient's mismatched molecule	One HLA-DQ-mismatch *n* = 324	Mortality	G1G1	32	1.0
				G1G2	148	1.32 (0.79 – 2.19; 0.29)
				G1G2	123	1.45 (0.86 – 2.44; 0.17)
				G2G2	21	1.35 (0.66 – 2.74; 0.41)
			II-IV Acute GVHD	G1G1	31	1.0
				G1G2	135	1.26 (0.56 – 2.83; 0.57)
				G1G2	119	1.05 (0.46 – 2.40; 0.91)
				G2G2	21	1.22 (0.38 – 3.85; 0.74)
			Chronic GVHD	G1G1	32	1.0
				G1G2	135	0.87 (0.49 – 1.53; 0.62)
				G1G2	117	1.35 (0.76 – 2.40; 0.31)
				G2G2	21	1.17 (0.51 – 2.70; 0.71)

F	Donor's mismatched molecule	Donors of the patients with one HLA-DQ mismatch *n* = 324	Relapse	G1G1 donor	43	1.0
				G1G2 donor	112	2.05 (0.95 – 4.43; 0.07)
				G1G2 donor	84	2.70 (1.27 – 5.73; 0.01)
				G2G2 donor	27	1.47 (0.57 – 3.81; 0.43)
			Disease-free survival	G1G1 donor	53	1.0
				G1G2 donor	133	1.38 (0.87 – 2.17; 0.17)
				G1G2 donor	100	1.56 (0.99 – 2.47; 0.06)
				G2G2 donor	30	1.29 (0.73 – 2.30; 0.38)
			Mortality	G1G1 donor	53	1.0
				G1G2 donor	138	1.14 (0.73 – 1.78; 0.58)
				G1G2 donor	102	1.22 (0.77 – 1.93; 0.40)
				G2G2 donor	31	1.16 (0.65 – 2.07; 0.61)
			II-IV Acute GVHD	G1G1 donor	52	1.0
				G1G2 donor	126	1.32 (0.64 – 2.74; 0.46)
				G1G2 donor	98	1.14 (0.54 – 2.40; 0.73)
				G2G2 donor	30	1.35 (0.53 – 3.44; 0.52)

			Chronic GVHD	G1G1 donor	52	1.0
				G1G2 donor	126	0.92 (0.52 – 1.61; 0.76)
				G1G2 donor	97	1.68 (0.97 – 2.91; 0.07)
				G2G2 donor	30	1.70 (0.86 – 3.38; 0.13)
G	Specific patient G1 mismatch	One G1 mismatch	Relapse	DQA1*02:01P-DQB1*03:03P	22	1.0
				DQA1*02:01P-DQB1*02:01P	16	1.75 (0.64 – 4.76; 0.27)
				DQA1*05:01P-DQB1*03:01P	11	0.72 (0.18 – 2.97; 0.65)
				DQA1*03:01P-DQB1*03:01P	31	0.55 (0.19 – 1.58; 0.27)
				DQA1*03:01P-DQB1*03:02P	46	0.62 (0.23 – 1.66; 0.34)
			Disease-free Survival	DQA1*02:01P-DQB1*03:03P	28	1.0
				DQA1*02:01P-DQB1*02:01P	18	0.82 (0.42 – 1.61; 0.57)
				DQA1*05:01P-DQB1*03:01P	15	0.49 (0.22 – 1.11; 0.09)
				DQA1*03:01P-DQB1*03:01P	37	0.50 (0.27 – 0.93; 0.03)
				DQA1*03:01P-DQB1*03:02P	51	0.66 (0.38 – 1.15; 0.14)
			Mortality	DQA1*02:01P*-DQB1*03:03P	29	1.0
				DQA1*02:01P-DQB1*02:01P	19	0.80 (0.40 – 1.60; 0.54)

				DQA1*05:01P-DQB1*03:01P	16	0.44 (0.18 – 1.05; 0.06)
				DQA1*03:01P-DQB1*03:01P	38	0.56 (0.30 – 1.04; 0.07)
				DQA1*03:01P-DQB1*03:02P	52	0.85 (0.49 – 1.47; 0.56)
			II-IV Acute GVHD	DQA1*02:01P-DQB1*03:03P	25	1.0
				DQA1*02:01P-DQB1*02:01P	16	0.31 (0.08 – 1.20; 0.09)
				DQA1*05:01P-DQB1*03:01P	16	0.40 (0.10 – 1.56; 0.19)
				DQA1*03:01P-DQB1*03:01P	36	0.34 (0.11 – 1.08; 0.07)
				DQA1*03:01P-DQB1*03:02P	49	0.38 (0.13 – 1.15; 0.09)
			Chronic GVHD	DQA1*02:01P-DQB1*03:03P	27	1.0
				DQA1*02:01P-DQB1*02:01P	17	0.59 (0.21 – 1.60; 0.30)
				DQA1*05:01P-DQB1*03:01P	16	0.93 (0.37 – 2.31; 0.88)
				DQA1*03:01P-DQB1*03:01P	34	0.66 (0.31 – 1.40; 0.27)
				DQA1*03:01P-DQB1*03:02P	49	0.45 (0.21 – 0.96; 0.04)
H	Specific patient G2 mismatch	One G2 mismatch	Relapse	DQA1*01:02P-DQB1*06:02P	23	1.0
				DQA1*01:02P-DQB1*06:03P	23	1.20 (0.48 – 2.97; 0.70)
				DQA1*01:02P-DQB1*06:04P	13	1.29 (0.48 – 3.49; 0.61)

				DQA1*01:02P-DQB1*05:02P	12	0.40 (0.08 – 1.91; 0.25)
			Disease-free survival	DQA1*01:02P-DQB1*06:02P	29	1.0
				DQA1*01:02P-DQB1*06:03P	26	1.19 (0.62 – 2.27; 0.60)
				DQA1*01:02P-DQB1*06:04P	16	1.42 (0.70 – 2.91; 0.33)
				DQA1*01:02P-DQB1*05:02P	14	0.90 (0.40 – 2.05; 0.81)
			Mortality	DQA1*01:02P-DQB1*06:02P	29	1.0
				DQA1*01:02P-DQB1*06:03P	26	1.30 (0.67 – 2.52; 0.43)
				DQA1*01:02P-DQB1*06:04P	16	0.94 (0.42 – 2.09; 0.87)
				DQA1*01:02P-DQB1*05:02P	14	1.01 (0.44 – 2.31; 0.99)

*The letter P following allele names (e.g. DQA1*03:01P) reflects that that particular allele is the chosen representative for the group of alleles that produce the same protein sequence at the antigen binding site despite having different sequences at other places in the protein.[2]

References for the Supplemental Data

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2. Robinson, J. et al. The IPD and IMGT/HLA database: allele variant databases. *Nucleic Acids Res.* **43**, D423-431 (2015).