Specific HLA-DQ G1/G2 mismatches affect myeloid malignancy relapse incidence in haploidentical HCT

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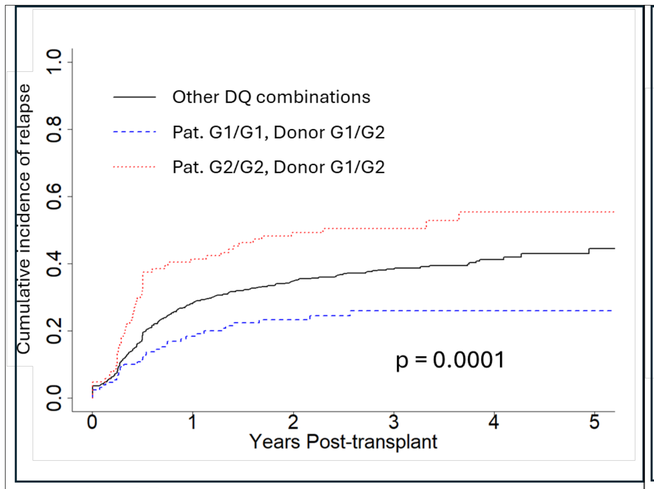
AIM

HLA-DQ G1 heterodimers comprise DQ2/3/4 antigens, which contain many peptide residues not found in G2 heterodimers (DQ5, DQ6). HLA-DQ has been indicated as particularly important to development of *de novo* antibody development and patient genotype content has been linked to relapse in studies of haploidentical and unrelated donors. We sought to determine if the HLA-DQ G1/G2 genotype of patients and donors affected relapse or other outcomes in publicly available CIBMTR data of haploidentical HCT cases.

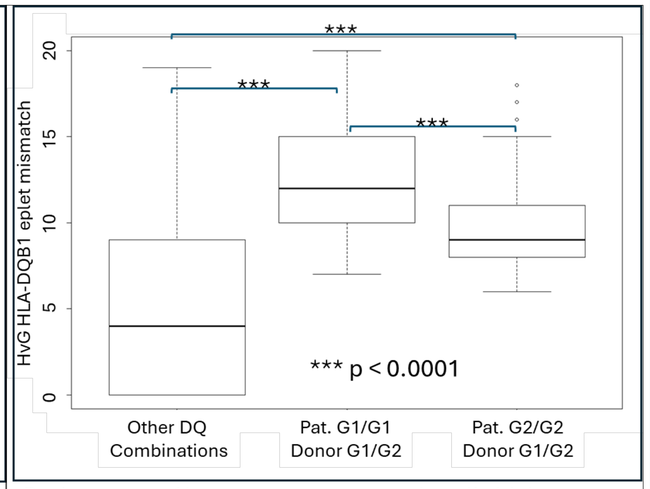
METHODS

We conducted a retrospective analysis using the publicly available P-5545 dataset of patients with haploidentical transplant with post-transplant cyclophosphamide from the Center for International Blood and Marrow Transplant Research (CIBMTR), available at https://cibmtr.org. The data set contained eplet analysis information performed by the original study authors. Data was analyzed with R studio v3.6.3 using *survival*, *cmprsk*, and *survminer* packages. Patients with missing relapse outcome were excluded (n = 23 of 1287).

Individual variables in the data set were assessed by univariate Fine and Grey analysis for association with relapse; variables with univariate $p < 0.1$ were included in an initial model, then reduced by backward stepwise regression until the model only included variables with $p < 0.05$.



Two HLA-DQ group mismatches between patient and donor show markedly different relapse rates from other match and mismatch combinations

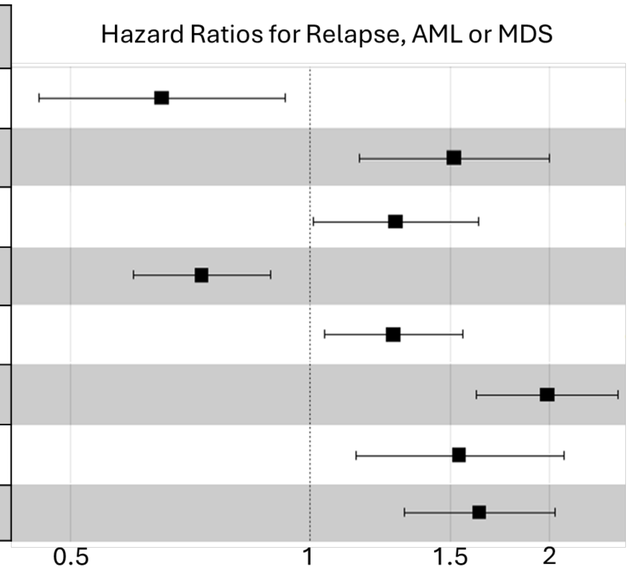


Both groups of interest create exceptionally high molecular (eplet) mismatch compared to other DQ match and mismatch groups.

After correction for other significant relapse risks in the data set, the HLA-DQ mismatch groups of interest remain independently associated with relapse risk.

Variable	Reference condition	Risk condition	HR (95% CI)	p
HLA-DQ	Other DQ combinations	Patient G1/G1, Donor G1/G2	0.65 (0.46-0.93)	0.02
HLA-DQ	Other DQ combinations	Patient G2/G2, Donor G1/G2	1.52 (1.15 – 2.0)	0.003
HLA-DR	GvH Mismatch	GvH match	1.28 (1.01 – 1.63)	0.04
Graft Type	Bone Marrow	PBSC	0.73 (0.60 – 0.89)	0.002
CMV serostatus	Any other or unknown†	Pat. Positive, Donor negative	1.27 (1.04 – 1.56)	0.02
Disease Risk Index	Low/Moderate	High or Very High	1.99 (1.62 – 2.44)	< 0.001
Disease Risk Index	Low/Moderate	Unknown or not classified‡	1.54 (1.14 – 2.08)	0.005
Conditioning	Myeloablative	RIC/NMA	1.63 (1.31 – 2.03)	< 0.001

† 7 cases unknown for CMV status
‡ 76 cases unknown; 40 MDS cases unclassified for DRI score



RESULTS

Most combinations of patient and donor HLA-DQ G1 and G2 genotypes had similar risks for outcomes, however, G1/G1 patients with G1/G2 donors (n = 164) had lower relapse incidence, while G2/G2 patients with G1/G2 donors (n = 124) had higher relapse rate. Interestingly, this effect was only observed in patients with myeloid malignancy (no relapse trend observed for the ALL subset). The effects on relapse for both combinations remained significant in multivariable analysis.

The group with reduced relapse also had a significant increase in NRM, which also remained significant after multivariable correction; the increased relapse group showed reduced NRM, but was not significant after correction. Furthermore, the DQ combinations associated with relapse had higher HLA-DQB1 eplet mismatch in the host-vs-graft direction than the reference group.

CONCLUSION

Our finding that two categories of HLA-DQ mismatch affected relapse risk in myeloid malignancy, but not ALL, contrasts with observations in prior studies. A previous report indicated that both G1/G1 and G2/G2 patients had lower relapse with G1/G2 donors, while we find relapse risk increased for the G2/G2 patients.

Although there is no clear mechanism for the observed effect, these findings may be useful in donor selection based on patient and donor HLA-DQ G1 and G2 genotypes.

ACKNOWLEDGEMENT AND DISCLAIMER

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