Accepted: 13 June 2017

DOI: 10.1111/ejh.12916

ORIGINAL ARTICLE

WILEY European Journal of Haematology

# Clinical outcomes of HLA-DPB1 mismatches in 10/10 HLA-matched unrelated donor-recipient pairs undergoing allogeneic stem cell transplant

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**Funding information**
This study was funded in part by Small Program Grants, Center for Clinical and Translational Science, Mayo Clinic, Rochester MN.

## Abstract

**Objective:** HLA-DPB1 matching may impact allogeneic hematopoietic stem cell transplantation (ASCT) outcomes; however, this locus is not in linkage disequilibrium with the remainder of the HLA genes. After classifying HLA-DPB1 mismatches based on T-cell epitope, avoiding non-permissive mismatches may impact survival. We tested this hypothesis at a single academic institution.

**Methods:** Retrospective HLA-DPB1 genotyping was performed on 153 adult patients who underwent ASCT and unrelated donors matched for HLA-A, B, C, DRB1, and DQB1 loci (10/10). Using the ImMunoGeneTics/HLA T-cell epitope matching algorithm, mismatch status was classified as permissive or non-permissive.

**Results:** Of 153 donor-recipient pairs, 22 (14.4%) were HLA-DPB1 matches, 64 (42.8%) permissive mismatches, and 67 (43.8%) non-permissive mismatches. DPB1 mismatch increased risk of chronic graft-versus-host disease (cGVHD; RR 2.89 [1.19-9.53], *P*=.016) compared with DPB1-matched transplants, but there were no differences in overall mortality, risk of relapse, or acute GVHD (aGVHD). Combining matches and permissive mismatches and comparing to non-permissive mismatches, there was no significant difference in overall survival or relapse; however, patients receiving non-permissive mismatched transplants experienced greater risk of aGVHD overall and severe aGVHD (RR 1.66 [1.13-2.44], *P*=.010 and RR 1.97 [1.10-3.59], *P*=.024, respectively).

**Conclusion:** In this single-center study, HLA-DPB1 matching influenced outcomes of patients undergoing ASCT for hematologic malignancy.

KEYWORDS

bone marrow transplantation, transplantation

## 1 | INTRODUCTION

In patients undergoing allogeneic hematopoietic stem cell transplant (ASCT), matching for human leukocyte antigens (HLA) between recipient and donor decreases the risks of graft-versus-host disease (GVHD), rejection, and mortality. As more sophisticated HLA-typing methods have replaced serology and low-resolution methods for matching, the overall survival has improved.[1] Currently, matching at HLA-A, HLA-B, HLA-C, HLA-DRB1, and DQB1 (10/10) is considered optimal, with a single mismatch at any non-DQB1 allele associated with 5%-10% increase in mortality and/or significant GVHD, whereas DQB1 mismatches are thought to be better tolerated.[2-10]

Recent literature has suggested that matching at the HLA-DPB1 locus, in addition to the standard loci, may impact outcomes in ASCT.[11-26] The β-chain of the HLA-DP antigen is known to be highly polymorphic, with 716 alleles encoding 591 proteins and 19 null variants, while the α-chain has 44 alleles encoding 22 proteins.[27] While many of the HLA genes are in tight linkage disequilibrium (LD), the degree of LD is much lower between HLA-DP and the remainder of the HLA cluster due to a recombination hot spot between the HLA-DQ and HLA-DP loci.[28] Retrospective studies of unrelated donor pairs report mismatch incidences of approximately 75%-90% at the HLA-DP locus.[11,13,16,20,29]

In donor-recipient pairs with HLA mismatch, whether the discrepancy is at the antigenic or the allele level may have clinical importance. Some HLA-DPB1 mismatches may be considered "permissive" when the expressed T-cell epitope structure is similar, thus, theoretically resulting in limited T-cell recognition due to similar T-cell receptor binding and cross-reactivity, while others could be considered "non-permissive" with greater differences in T-cell epitope structure, which may put the recipient at increased risk of suboptimal outcome.[13,16,21,23] A requirement to match for HLA-DP would decrease the number of eligible donors for an individual significantly, due to the low degree of LD. Therefore, rather than matching at the DPB1 allele level, tools can be used to classify the T-cell epitopes (TCE) that are expressed by the donor and recipient and to predict whether a mismatch is permissive or non-permissive.[30] Another recent approach assigns functional distance scores based on the combined impact of polymorphic amino acids to determine which mismatches may be more likely to result in suboptimal outcomes.[22] Using a system to identify and avoid only mismatches that result in poorer clinical outcomes and allowing tolerated mismatches may allow for more donors to be eligible while yet keeping potential risks associated with a mismatch at an acceptable level.

Although a number of studies have suggested a relationship between HLA-DPB1 mismatch (or non-permissive mismatch) and suboptimal transplant outcomes, there are discordant studies, and matching at this locus is not always included in donor selection algorithms.[12-21] Because of the large degree of population differences in the HLA system, as well as variability in conditioning regimens and GVHD prophylaxis across institutions, selecting a large cohort of similar patients for reliable comparisons of outcomes in patients is challenging and may explain some of the differences in findings. Therefore, to better understand the importance of HLA-DPB1 matching, we performed a retrospective study evaluating outcomes in patients genotyped for HLA-DPB1 at our institution.

## 2 | PATIENTS AND METHODS/MATERIALS

### 2.1 | Subjects

This retrospective chart review study included 153 consecutive adult patients who underwent primary allogeneic HSCT for hematologic malignancies at Mayo Clinic in Rochester, MN between January 1, 2008, and May 25, 2013. Patients were matched as per usual clinical practice for the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci without consideration of the HLA-DPB1 locus. Patients were followed for a median of 755 days from the date of transplant (mean 844 days, range 11 to 2427 days). Clinical data were obtained from the Mayo Clinic electronic medical record system. This study was approved by the Mayo Clinic Institutional Review Board.

### 2.2 | HLA typing

Patient and donor HLA genotyping was resolved at high resolution (2nd field) or allele level typing by a combination of Luminex technology applied to PCR-based sequence-specific oligonucleotide (SSO) typing methodology using the One Lambda LABType SSO Class I and Class II typing kits (Thermo Fischer Scientific, Canoga Park, CA, USA) and commercial sequence-specific primer amplification typing kits (Olerup Inc., West Chester, PA, USA). An online tool, the DPB1 T-Cell Epitope Matching Algorithm v2.0, available through the ImMunoGeneTics/HLA (IMGT/HLA) website (http://www.ebi.ac.uk/ipd/imgt/hla/dpb.html) was utilized to predict the immunogenicity and classify donor-recipient pairs into permissive or non-permissive status.[13,21,23,30-33]

### 2.3 | Statistical analysis

All statistical analyses were performed using JMP (v.10.0.0) software (SAS Institute Inc., Cary, NC, USA). The association between HLA-DPB1 matching status and clinical outcomes was assessed using Kaplan-Meier methods and Cox proportional hazards models. *P*-value ≤.05 was considered statistically significant. In multivariate analyses, outcomes were adjusted for covariates associated with outcome as determined by a stepwise backward elimination approach. Covariates under consideration included diagnosis (lymphoid vs myeloid malignancy), conditioning regimen (myeloablative vs non-myeloablative/reduced intensity), T-cell depletion (by administration of antithymocyte globulin or alemtuzumab), ABO incompatibility, age at transplant, sex match vs mismatch, graft type (peripheral blood stem cells vs bone marrow), donor age, and GVHD prophylaxis.

## 3 | RESULTS

### 3.1 | Demographics

Patient and donor characteristics are shown in Table 1. The specific IBMTR diagnoses for patients with lymphoid malignancy included 20 patients with acute lymphoblastic leukemia, four with non-Hodgkin lymphoma, 10 with plasma cell disorders, and 20 with other leukemias;

**TABLE 1** Patient and donor characteristics. Matched, permissive mismatch, and non-permissive mismatch refer to matching status at the HLA-DPB1 locus as determined by the DPB1 T-Cell Epitope Matching Algorithm v2.0, available through the ImMunoGeneTics/HLA (IMGT/HLA) website. P-values are given for the association between DPB1 matching status and each parameter. Data in table refer to number of patients, aside from recipient age and donor age, which are given as mean (range) for the group

| | Matched | Permissive mismatch | Non-permissive mismatch | *P* |
|---|---|---|---|---|
| n | 22 | 64 | 67 (26 GvH, 41 HvG) | |
| Recipient age (years) [mean (range)] | 49.4 (18-61) | 49.8 (24-68) | 49.8 (24-68) | .99 |
| Diagnosis | | | | |
| Myeloid | 16 | 40 | 42 | .65 |
| Lymphoid | 6 | 24 | 25 | |
| Disease status at transplant | | | | |
| Clinical remission | 14 | 31 | 37 | .45 |
| Not in remission | 6 | 30 | 24 | |
| Unknown | 2 | 3 | 6 | |
| Recipient-donor sex | | | | |
| Male-male | 10 | 32 | 22 | .09 |
| Male-female | 2 | 6 | 4 | |
| Female-male | 3 | 18 | 21 | |
| Female-female | 7 | 8 | 20 | |
| Donor age (years) [mean(range)] | 30.3 (19-48) | 30.5 (19-57) | 33.0 (19-59) | .29 |
| ABO incompatibility | | | | |
| None | 6 | 31 | 38 | .32 |
| Minor | 8 | 15 | 11 | |
| Major | 7 | 17 | 17 | |
| Both | 1 | 1 | 1 | |
| Source of cells | | | | |
| Bone marrow | 1 | 7 | 8 | .55 |
| Peripheral blood stem cells | 21 | 57 | 59 | |
| Conditioning | | | | |
| Myeloablative | 13 | 27 | 25 | .20 |
| Non-myeloablative/ reduced intensity | 9 | 37 | 42 | |
| T-cell depletion | | | | |
| Yes | 1 | 3 | 2 | .87 |
| No | 21 | 61 | 65 | |
| GVHD prophylaxis | | | | |
| Tacrolimus/ Methotrexate | 18 | 56 | 53 | .53 |
| Tacrolimus/ Mycophenolate | 2 | 6 | 7 | |
| Other | 2 | 2 | 7 | |

among the patients with myeloid malignancy, the diagnoses included 55 patients with acute myelogenous leukemia, eight with chronic myelogenous leukemia, and 36 with myelodysplastic/myeloproliferative disorders. Of the 153 donor-recipient pairs, 22 (14.4%) were matched at HLA-DBP1, while 64 (42.8%) were classified as permissive mismatches, and 67 (43.8%) were classified as non-permissive mismatches by the DPB1 T-Cell Epitope Matching Algorithm v2.0. Among those classified as non-permissive mismatches, 26 were in the graft-versus-host direction, while 41 were in the host-versus-graft direction, with no bidirectional mismatches. Of the 153 recipients, 75 (49.0%) died, 32 (20.9%) experienced disease relapse, 106 (69.3%) developed acute GVHD (aGVHD) (any grade), 45 (29.4%) developed severe (grade III-IV) aGVHD, and 85 (55.6%) developed chronic GVHD (cGVHD; any severity) during the follow-up period.

**TABLE 2** Univariate analyses (A) and multivariate analyses (B) demonstrating impact of any mismatch, permissive mismatch, or non-permissive mismatch on overall mortality, relapse, any aGVHD, severe aGVHD, and cGVHD, compared to HLA-DPB1 match, or comparing non-permissive mismatch to permissive mismatch

| | Any mismatch[a] RR (CI), *P*-value | Permissive mismatch[a] RR (CI), *P*-value | Non-permissive mismatch[a] RR (CI), *P*-value | Non-permissive mismatch[b] RR (CI), *P*-value |
|---|---|---|---|---|
| (A) | | | | |
| Overall mortality | 0.95 (0.53-1.91), .89 | 0.79 (0.40-1.65), .51 | 1.14 (0.60-2.36), .69 | 1.45 (0.89-2.40), .14 |
| Relapse | 1.08 (0.42-3.66), .88 | 0.98 (0.34-3.46), .96 | 1.20 (0.43-4.20), .74 | 1.23 (0.58-2.62), .59 |
| aGVHD | 0.87 (0.52-1.57), .63 | 0.63 (0.35-1.19), .15 | 1.18 (0.68-2.16), .57 | 1.86 (1.23-2.85), .0034 |
| aGVHD (grade III-IV) | 0.70 (0.34-1.61), .37 | 0.41 (0.17-1.04), .06 | 1.05 (0.50-2.50), .90 | 2.59 (1.33-5.34), .0050 |
| cGVHD | 2.89 (1.19-9.53), .016 | 3.20 (1.27-10.7), .011 | 2.58 (1.01-8.72), .048 | 0.80 (0.49-1.32), .39 |
| (B) | | | | |
| Overall mortality | 0.94 (0.52-1.89), .86 | 0.80 (0.41-1.68), .53 | 1.22 (0.64-2.54), .55 | 1.53 (0.93-2.54), .09 |
| Relapse | 0.97 (0.37-3.28), .95 | 1.08 (0.35-4.73), .90 | 1.34 (0.44-5.84), .63 | 1.24 (0.59-2.66), .57 |
| aGVHD | 0.96 (0.57-1.73), .88 | 0.67 (0.38-1.27), .21 | 1.39 (0.80-2.58), .25 | 2.07 (1.36-3.19), .0007 |
| aGVHD (grade III-IV) | 0.89 (0.43-2.07), .77 | 0.49 (0.20-1.27), .14 | 1.50 (0.70-3.60), .31 | 3.04 (1.55-6.30), .0011 |
| cGVHD | 3.14 (1.29-10.38), .009 | 3.42 (1.36-11.50), .007 | 2.85 (1.11-9.67), .027 | 0.83 (0.50-1.37), .48 |

[a]Match as reference.
[b]Permissive mismatch as reference.

### 3.2 | Impact of any DPB1 mismatch on outcomes

In univariate analyses, recipients of a transplant with any DPB1 mismatch compared to complete DPB1 match experienced increased risk of chronic (cGVHD) (RR 2.89 [95% CI=1.19-9.53], *P*=.016), but no differences in overall mortality (RR 0.95 [0.53-1.91], *P*=.89), relapse (RR 1.08 [0.42-3.66], *P*=.88), acute GVHD (aGVHD) (RR 0.87 [0.52-1.57], *P*=.63), or severe (grades III-IV) aGVHD (RR 0.70 [0.34-1.61], *P*=.37; Table 2A). After adjusting for the covariates of diagnosis (lymphoid vs myeloid) and graft type (peripheral blood stem cells vs marrow), any DPB1 mismatch was still significantly associated with increased risk of cGVHD (RR 3.14 [1.29-10.38], ***P***=.009; Table 2B). In contrast, after adjusting for covariates selected by stepwise backward elimination for each outcome, there were no differences in other outcomes of patients receiving matched vs any DPB1-mismatched transplant (all ***P***>.05).

### 3.3 | Impact of non-permissive DPB1 mismatch on outcomes

Next, patients who received an ASCT that was matched at HLA-DPB1 and patients who received a transplant that was a permissive DPB1 mismatch were combined into one group and compared to those who received a transplant that was a non-permissive HLA-DPB1 mismatch. In univariate analyses, patients who received non-permissive DPB1-mismatched transplants were more likely to experience acute GVHD and severe (grade III-IV) aGVHD compared with those receiving matched or permissive mismatched transplants (RR 1.66 [1.13-2.44], *P*=.010 and RR 1.97 [1.10-3.59], *P*=.024, respectively, Figure 1). When non-permissive DPB1 mismatches were further classified by whether the mismatch was in the graft-versus-host (GvH) or host-versus-graft (HvG) direction, non-permissive mismatches in the GvH direction carried greater risk of development of aGVHD or severe aGVHD than those in the HvG direction (1.46 [0.84-2.51], *P*=.17 for aGVHD and 2.46 [1.12-5.55], *P*=.026 for severe aGVHD, Figure 2). In a multivariate model, after adjusting for ABO incompatibility and sex mismatch between donor and recipient, the risk of development of aGVHD (RR 1.88 [1.27-2.77], *P*=.0016) or severe (grade III-IV) aGVHD (RR 2.52 [1.39-4.64], *P*=.0024) remained significantly higher for those with a non-permissive DPB1 mismatch compared with those receiving a matched or permissive mismatched transplant. There were no significant differences in overall survival (RR 1.36 [0.86-2.15], *P*=.18), relapse (RR 1.22 [0.60-2.45], *P*=.57), time to neutrophil engraftment (1.03 [0.74-1.42], *P*=.88), time to platelet engraftment (0.93 [0.65-1.31], *P*=.68), or chronic GVHD (0.98 [0.60-1.60], *P*=.95) among those receiving non-permissive mismatched transplants vs those receiving DPB1-matched or permissive mismatched transplants (Figure 1).

In contrast, when the reference group was limited to HLA-DPB1-matched transplants (without including the permissive mismatched transplants), we found that non-permissive mismatch was significantly associated with increased risk of cGVHD (univariate RR 2.58 [1.01-8.72], *P*=.048 and multivariate RR 2.85 [1.11-9.67], *P*=.27), but not aGVHD, overall mortality, or relapse in both univariate (Table 2A) and multivariate analyses (Table 2B). When comparing non-permissive mismatches to only permissive mismatches, we again found a significantly increased risk of any and severe aGVHD in univariate analyses (1.86 [1.23-5.34], *P*=.003 and 2.59 [1.33-5.34], *P*=.005, respectively) and in multivariate analyses (2.07 [1.36-3.19], *P*=.001 and 3.04 [1.55-6.30], *P*=.001, respectively), but no difference in cGVHD.

Finally, we also evaluated whether there were differences in non-relapse mortality among patients with HLA-DPB1-matched/permissive mismatched transplants vs those who received a non-permissive mismatched transplant (Figure 3). Non-relapse mortality was higher in the first year among patients with non-permissive

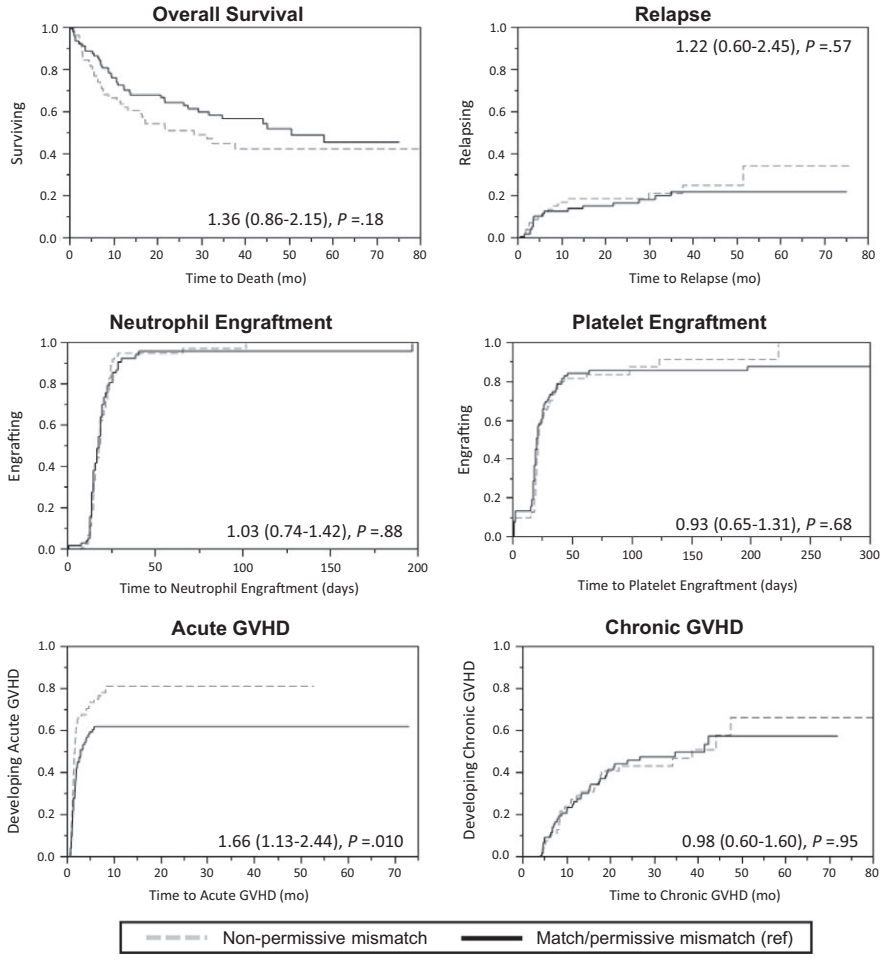
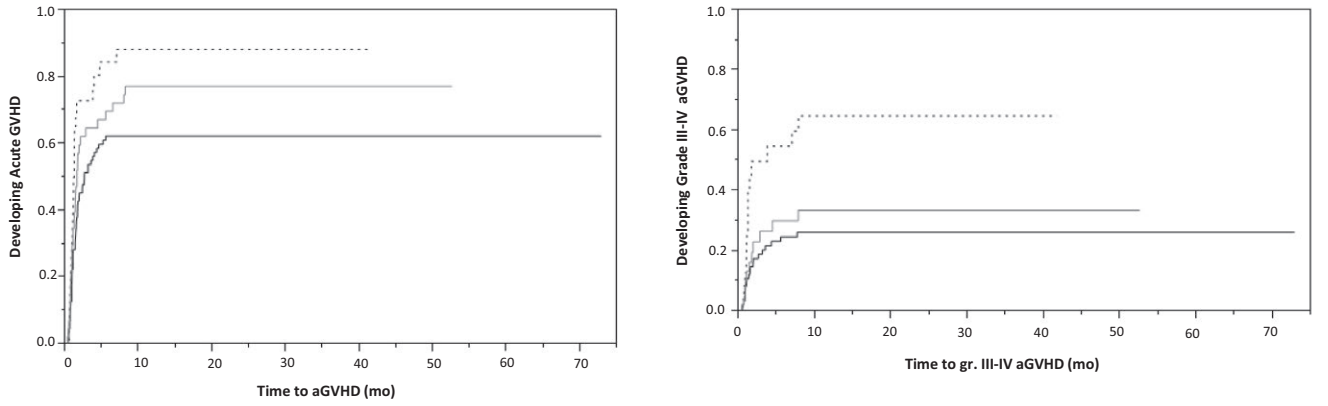



**FIGURE 1** Comparison between HLA-DPB1 non-permissive mismatches vs matches/permissive mismatches on clinically important outcomes. Kaplan-Meier curve and risk ratio (along with 95% confidence interval in parentheses) are given for each parameter along with *P*-value

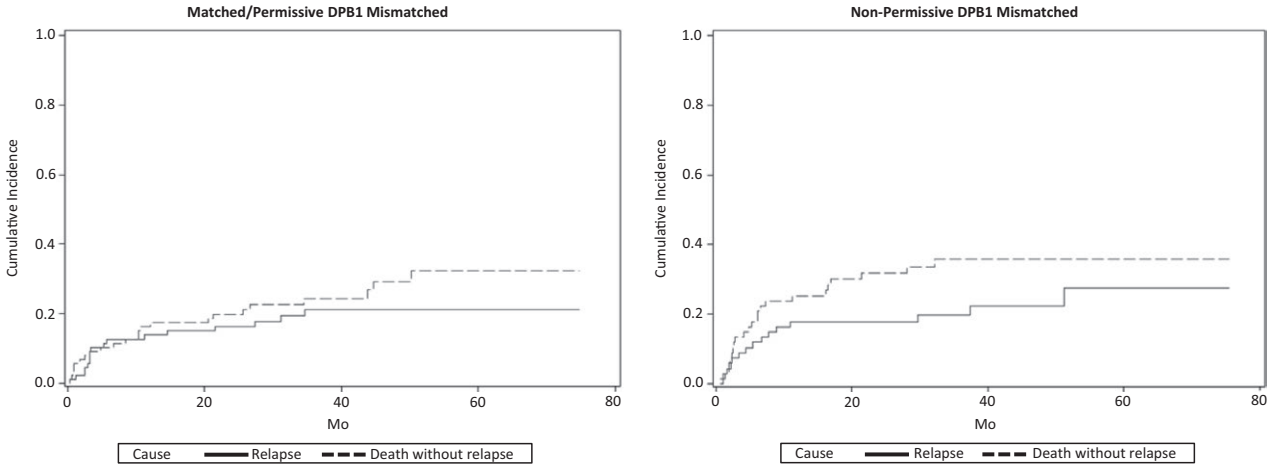



| | GvH* | HvG* | GvH vs HvG |
|---|---|---|---|
| Acute GVHD | 2.11 (1.26-3.41), *P* = .005 | 1.44 (0.91-2.23), *P* = .12 | 1.46 (0.84-2.51), *P* = .17 |
| Grade III-IV AGVHD | 3.24 (1.60-6.40), *P* = .002 | 1.32 (0.61-2.71), *P* = .47 | 2.46 (1.12-5.55), *P* = .026 |

*Type of non-permissive mismatch; Match/permissive mismatch as reference

**FIGURE 2** Comparison between HLA-DPB1 match/permissive mismatches vs non-permissive mismatches in the graft-versus-host (GvH) direction vs mismatches in the host-versus-graft (HvG) direction on acute graft-versus-host disease. Kaplan-Meier curve and risk ratio (along with 95% confidence interval in parentheses) are given for each parameter along with *P*-value. Risk ratios are estimated for non-permissive mismatches in the GvH and the HvG directions relative to a reference group consisting of matches and permissive mismatches

transplants (cumulative incidence [CI] .254) than patients with permissive transplants (CI .163), but was similar by year 5 (CI .325 vs .358). Relapse rates were slightly higher among patients with non-permissive transplant throughout the study (CI for non-permissive .179 at year 1 and .277 at year 7 vs .140 at year 1 and .211 at year 7 among those with DPB1-matched/permissive transplants).




| Year | Cumulative Incidence - Death without Relapse | | Cumulative Incidence - Relapse | |
|---|---|---|---|---|
| | Matched/Permissive | Non-Permissive | Matched/Permissive | Non-Permissive |
| 1 | 0.163 | 0.254 | 0.14 | 0.179 |
| 2 | 0.199 | 0.318 | 0.164 | 0.179 |
| 3 | 0.244 | 0.358 | 0.211 | 0.198 |
| 4 | 0.294 | 0.358 | 0.211 | 0.225 |
| 5 | 0.325 | 0.358 | 0.211 | 0.277 |
| 6 | 0.325 | 0.358 | 0.211 | 0.277 |
| 7 | 0.325 | 0.358 | 0.211 | 0.277 |

**FIGURE 3** Non-relapse mortality in HLA-DPB1 matches/permissive mismatches vs non-permissive mismatches. Kaplan-Meier curves and cumulative incidence for both relapse and death without relapse throughout the study period are provided

### 3.4 | Permissive DPB1 mismatch compared with DPB1 match

Although permissive DPB1-mismatched ASCT is expected to have similar outcomes to DPB1-matched ASCT, we found in our univariate analyses that patients receiving permissive mismatched transplants were more likely to develop cGVHD (RR 3.20 [1.27-10.7], *P*=.011) than patients receiving DPB1-matched transplants (Table 2A). In multivariate analyses, the relationship between permissive DPB1 mismatch vs DPB1 match and cGVHD remained significant (RR 3.42 [1.36-11.50], *P*=.007) after adjustment for diagnosis (myeloid vs lymphoid malignancy) and graft type (peripheral blood stem cells vs bone marrow) (Table 2B). No significant differences in overall mortality, relapse, or aGVHD were observed between permissive DPB1-mismatched transplants and DPB1-matched transplants in univariate or multivariate analyses.

## 4 | DISCUSSION

In this retrospective single institution study, we found that among patients receiving ASCT for hematologic malignancies, those receiving any HLA-DPB1-mismatched transplant had a higher risk of cGVHD, but not overall mortality, risk of relapse, or aGVHD. After classification of mismatches into non-permissive and permissive based on predicted structural similarities among proteins encoded by the various haplotypes, we found that patients receiving a non-permissive HLA-DPB1 mismatch had an increased risk of any aGVHD as well as severe (grade III-IV) aGVHD when compared to the combined group of matched and permissive mismatched transplants. Furthermore, when compared to only DPB1-matched transplants as a reference group, both the permissive mismatched and the non-permissive mismatched groups showed an increased risk of cGVHD, but no increased risk of aGVHD. Compared to the permissive mismatches, the non-permissive mismatches showed an increased risk of both any aGVHD and severe aGVHD, but no difference in risk of cGVHD. These findings demonstrate that permissive mismatches and matches are not entirely equivalent. Our observations may in part be explained by the extent of TCE dissimilarity having differing impact on the outcomes studied. For example, perhaps in the setting of a permissive mismatch, the differences in TCE are small enough to not acutely result in GVHD, but over time an increasing immune response may be generated, whereas the greater differences in TCE in non-permissive mismatches result in a more vigorous immune response early after transplant, resulting in more cases of aGVHD. However, basic science research studies will be required to fully elucidate the underlying biology of these observations.

Previous reports have come to conflicting conclusions related to the clinical impact of DPB1 mismatches and permissivity. Similar to recent studies by Zino et al. and Fleischhauer et al., we found that patients receiving a non-permissive HLA-DPB1 mismatch were at increased risk of aGVHD;[13,21] however, we did not observe the increase in mortality found in these studies. In addition, we observed a higher risk of developing chronic GVHD among patients who received any HLA-DPB1 mismatch, regardless of the permissivity status. Furthermore, this increase in chronic GVHD appears to be in part driven by patients who received a permissive HLA-DPB1-mismatched

transplant. We are not aware of any other studies demonstrating this novel relationship. Conflicting results among studies may occur for a variety of reasons, including different donor/recipient populations and variation in local treatment practices (including conditioning regimens and GVHD prophylaxis). In addition to further understanding and resolving these conflicting results, in future studies it may also be important to evaluate the impact of HLA-DPB1 mismatches specifically among patients receiving cytolytic T-lymphocyte immunotherapy after ASCT. Recent studies have found that HLA-class II-restricted CD4+ T-cells can exert cytolytic activity toward leukemia cells, and that it may be possible to utilize the immunogenicity of an HLA-DPB1 mismatch for a more selective graft-versus-leukemia effect.[34]

Although our study is helpful in better understanding the impact of HLA-DPB1 matching in a single academic institution and specifically on our local practice, it has several limitations. While all adult patients receiving ASCT for hematologic malignancies between 2008 and 2013 were included, this number only totaled 153. Therefore, our numbers are modest for analyses of subgroups, such as permissive vs non-permissive mismatches as well as the directionality of the mismatch. In addition, recent studies have identified a SNP that alters expression of HLA-DPB1 protein, which also impacts the immunogenicity.[33] Our data do not include genetic variants that influence expression.

In conclusion, we found that at our experienced academic center which has favorable outcomes, additional matching for HLA-DPB1 epitopes may influence outcomes—particularly related to acute and chronic GVHD—of patients undergoing allogeneic hematopoietic stem cell transplant for hematologic malignancy. In addition, matching at HLA-DPB1 may be important in the avoidance of cGVHD.

## ACKNOWLEDGEMENT

The authors would like to thank LeAnn Batterson for her assistance with acquiring clinical data for this study.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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**How to cite this article:** Moyer AM, Hashmi SK, Kroning CM, et al. Clinical outcomes of HLA-DPB1 mismatches in 10/10 HLA-matched unrelated donor-recipient pairs undergoing allogeneic stem cell transplant. *Eur J Haematol*. 2017;00:1–8. https://doi.org/10.1111/ejh.12916