Patient HLA Germline Variation and Transplant Survivorship


ABSTRACT

Purpose

HLA mismatching increases mortality after unrelated donor hematopoietic cell transplantation. The role of the patient’s germline variation on survival is not known.

Patients and Methods

We previously identified 12 single nucleotide polymorphisms within the HLA region as markers of transplantation determinants and tested these in an independent cohort of 1,555 HLA-mismatched unrelated transplants. Linkage disequilibrium mapping across class II identified candidate susceptibility features. The candidate gene was confirmed in an independent cohort of 3,061 patients.

Results

Patient rs429916AA/AC was associated with increased transplantation-related mortality compared with rs429916CC (hazard ratio [HR], 1.39; 95% CI, 1.12 to 1.73; $P = .003$); rs429916A positivity was a proxy for DOA*01:01:05. Mortality increased with one (HR, 1.17; 95% CI, 1.0 to 1.36; $P = .05$) and two (HR, 2.51; 95% CI, 1.41 to 4.45; $P = .002$) DOA*01:01:05 alleles. HLA-DOA*01:01:05 was a proxy for HLA-DRB1 alleles encoding FEY (HR $< 10^{-15}$) and FDH (HR $< 10^{-15}$) amino acid substitutions at residues 26/28/30 that influence HLA-DRB peptide repertoire. FEY- and FDH-positive alleles were positively associated with rs429916A (HR $< 10^{-15}$); FDY-positive alleles were negatively associated. Mortality was increased with FEY (HR, 1.66; 95% CI, 1.29 to 2.13; $P = .00008$) and FDH (HR, 1.40; 95% CI, 1.02 to 1.93; $P = .04$), whereas FDY was protective (HR, 0.88; 95% CI, 0.78 to 0.98; $P = .02$). Of the three candidate motifs, FEY was validated as the susceptibility determinant for mortality (HR, 1.29; 95% CI, 1.00 to 1.67; $P = .05$). Although FEY was found frequently among African and Hispanic Americans, it increased mortality independently of ancestry.

Conclusion

Patient germline HLA-DRB1 alleles that encode amino acid substitutions that influence the peptide repertoire of HLA-DRB predispose to increased death after transplantation. Patient germline variation informs transplantation outcomes across US populations and may provide a means to reduce risks for high-risk patients through pretransplantation screening and evaluation.

J Clin Oncol 36:2524-2531. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Transplantation outcomes can be shaped by the clinical features of the patient, the donor, and the transplantation procedure itself. Efforts to improve the success of transplantation focus on optimizing modifiable factors, including better control of the patient’s disease before transplantation to lower disease recurrence, complete donor matching of HLA genes to lower the risk of graft-versus-host disease, and the use of less-intensive conditioning regimens to lower organ toxicity.1-3

A patient’s inherited genome (germline) represents a nonmodifiable characteristic that is increasingly recognized as an important factor in shaping health outcomes. Germline variation may affect not only predisposition to disease but also host response to disease and therapeutic interventions.4,5 The major histocompatibility complex (MHC) encodes the highest density of genes with immune-related function in the human genome and is a candidate region for genes that influence transplantation outcomes; however, a comprehensive and systematic analysis of the clinical importance of non-HLA sequence variation within the MHC is lacking.6-8

We tested the hypothesis that germline variation within the highly polymorphic MHC can impart risks to patients who undergo hematopoietic cell transplantation from HLA-mismatched donors that are not explained by patient-donor...
HLA mismatching. We previously used MHC region single nucleotide polymorphisms (SNPs) and identified 12 candidate transplantation determinants.9 The 12 SNPs gave rise to 14 associations—11 associations that involve 11 SNPs each with one clinical end point for either patient genotype, donor genotype, or patient-donor mismatch and three associations that involve one SNP with three clinical end points for patient genotype. In the current study, we conducted a multistage validation to confirm the susceptibility SNP and identify the true causative gene. Knowledge of clinically relevant germline variation may provide insight into a genetic component of transplantation survivorship and the possible mechanisms that shape an individual patient’s outcome.

**PATIENTS AND METHODS**

**Study Design and Population**

Each of the 14 previously identified associations (cohort 1)9 was tested in an independent cohort (cohort 2) of 1,553 transplantations with one HLA-A, -B, -C, -DRB1, or -DQB1 mismatch (Fig 1; Data Supplement). Of the 14 hypotheses, patient rs429916 genotype was validated as a marker for transplantation-related mortality. No associations were found between donor SNP genotype or patient-donor SNP mismatching (Data Supplement). Subsequently, fine-mapping of rs429916 was performed in 3,397 patients with residual DNA (2,052 from cohort 1 and 1,345 from cohort 2 [fine-mapping cohort]), and the candidate causative gene HLA-DRB1 was identified. An independent cohort of 3,061 transplantations with one HLA mismatch (cohort 3; Data Supplement) was then studied to confirm the HLA-DRB1 results (Fig 1). All patients provided informed consent for participation in this study. Clinical data were reported to the Center for International Blood and Marrow Transplant Research, and pretransplantation samples were provided from the Center for International Blood and Marrow Transplant Research Repository. Protocols were approved by the institutional review boards of the Fred Hutchinson Cancer Research Center and the National Marrow Donor Program.

**Genotyping and Expression Studies**

HLA genes and SNPs were genotyped and quantitative polymerase chain reaction and RNA sequencing performed as previously described2,8,10 (Data Supplement). Linkage disequilibrium (LD; D', r, and r²) between markers was estimated with Haploview, PLINK version 1.07, and R Package genetics version 1.3.8.1, as previously described.9

**Statistical Analysis**

Criteria for SNP validation in cohort 2 required association with the same end point in the same genetic variant form as previously observed in cohort 1.9 Outcomes were assessed using Cox proportional hazards.
regression models, which model the cause-specific hazards with competing events treated as censored. For each adjusted covariate, unknown data were excluded from regression models if there were fewer than 10 cases; otherwise, missing data were treated as a separate group. Proportional hazards were examined for all clinical covariates using a time-dependent covariate approach.

Factors that violated proportional hazards were adjusted through stratification. Stepwise forward-backward model selection was used to identify clinical prognostic risk factors as well as HLA allele or antigen mismatches at a 5% significance level. To assess whether a particular HLA allele may influence a clinical end point, comparison of genotypes with zero, one, or two copies of the allele in patients and donors were made at a 1% significance level. Finally, each SNP was tested separately by forcing the SNP into the multivariable model with an adjustment for the identified variables (Data Supplement). To adjust for multiple testing of 14 hypotheses for the 12 SNPs, the Bonferroni’s threshold of 0.0036 was used to indicate statistical significance. Fine-mapping and validation of the at-risk gene used Cox regression models to compare the hazards of failure with the possession of the number of copies of HLA-DOA allele, HLA-DRB1 alleles, and HLA-DRB3 residues. P values from Cox proportional hazards regression modeling were obtained from the Wald test. All P values are two sided. Data analyses were performed using SAS 9.3 statistical software (SAS Institute, Cary, NC).

## RESULTS

### Patient rs429916 AA Genotype and Mortality

Of the 14 hypotheses, the association of patient rs429916 genotype with transplantation-related mortality was validated (Fig 1; Table 1; Data Supplement). Patients with rs429916AA and -AC genotypes had a higher 1- and 2-year transplantation-related mortality (45% and 50%, respectively) than those with rs429916CC (31% and 37%, respectively) and higher hazards of transplantation-related mortality (hazard ratio [HR], 1.39; 95% CI, 1.12 to 1.73; P = .003). In the fine-mapping cohort, the risks of both transplantation-related mortality and mortality increased with increasing numbers of rs429916A, consistent with a biologic step-up of risks (Table 1).

The rs429916 genotype resides in a haplotype block that includes only HLA-DOA (Fig 2). HLA-DOA encodes the DOα heterodimer of HLA-DO, a natural inhibitor of HLA-DM involved in peptide loading of class II molecules. Three DOA proteins, DOA*01:01, DOA*01:02, and DOA*01:03, are recognized. DOA*01:01 is encoded by DOA*01:01:01 to 01:01:06 distincted by silent substitutions. Among known DOA alleles, only DOA*01:01:05 is in strong positive LD with rs429916A (D’, 0.80; r, +0.60; P < 10E-15), which suggests that rs429916A and DOA*01:01:05 are proxies for each other (Data Supplement). Among 292 HLA-DOA*01:01:05-positive patients, 249 (85%) had rs429916A; among 5,105 HLA-DOA*01:01:05-negative patients, only 255 (8%) had rs429916A (P < 2.2E-16). In contrast, rs429916A positivity was observed in only 8% of DOA*01:01:01/03-, 14% of DOA*01:01:02/04-, 4% of DOA*01:01:06-, and 11% of DOA*01:02-positive patients (Data Supplement).

In 1000 Genomes populations with rs429916 genotype and data that enable assignment of WHO-recognized HLA-DOA alleles, DOA*01:01:05 is in strong positive LD with rs429916A (D’, 0.96; r, +0.60; P < 10E-15), whereas all other

| Table 1. Multivariable Models for Transplantation-Related Mortality and Mortality According to Patient rs429916 Genotype in Cohort 1, Cohort 2, and the Fine-Mapping Cohort |
|-----------------|-----------------|-----------------|
| Cohort          | Clinical End Point | Overall P | Patient rs429916 Genotype | No. | HR (95% CI) | P   |
|                 |                  |            | CC                         |     |            |     |
| Cohort 1‡       | Overall mortality | <.001      | CC                         | 1,909 | 1          |     |
|                 |                  |            | AC                         | 296  | 1.11 (0.94 to 1.31) | .230 |
|                 |                  |            | AA                         | 19   | 3.47 (1.95 to 6.16) | <.001 |
| Disease-free survival |          |            | CC                         | 1,708 | 1          |     |
|                 |                  |            | AC                         | 268  | 1.06 (0.88 to 1.26) | .560 |
|                 |                  |            | AA                         | 19   | 3.75 (2.10 to 6.68) | <.001 |
| Transplantation-related mortality |          | <.001      | CC                         | 1,696 | 1          |     |
|                 |                  |            | AC                         | 267  | 1.20 (0.97 to 1.49) | .10  |
|                 |                  |            | AA                         | 19   | 4.52 (2.31 to 8.86) | <.001 |
| Cohort 2         | Transplantation-related mortality | .003 | CC                         | 1,107 | 1          |     |
|                 |                  |            | AC + AA‡                    | 196  | 1.39 (1.12 to 1.73) | .003 |
| Fine-mapping cohort 1 and 2 | Overall mortality | <.001      | CC                         | 2,882 | 1          |     |
|                 |                  |            | AC                         | 474  | 1.16 (1.03 to 1.31) | .010 |
|                 |                  |            | AA                         | 29   | 2.12 (1.40 to 3.22) | <.001 |
| Transplantation-related mortality |          <.001 |    | CC                         | 2,882 | 1          |     |
|                 |                  |            | AC                         | 474  | 1.24 (1.07 to 1.43) | .004 |
|                 |                  |            | AA                         | 29   | 2.13 (1.28 to 3.86) | .005 |

NOTE. As previously described, patient rs429916 genotype correlates with the risks of overall mortality, disease-free survival, and transplantation-related mortality in the discovery cohort (cohort 1). In the current study, the association between patient rs429916 genotype and transplantation-related mortality and mortality was confirmed in cohort 2. Fine-mapping to identify the causative gene was performed in cohorts 1 and 2 with sufficient residual DNA. Adjusted variables used for cohort 1 models were previously described. For cohort 2, the transplantation-related mortality model was adjusted for patient age, disease stage, graft-versus-host disease prophylaxis, Karnofsky performance score, copy number of patient’s DRB1*13, and patient-donor allele mismatching at HLA-A, -B, and -C and stratified by graft type. For the combined cohorts 1 and 2, the overall mortality model was adjusted for patient-donor cytomegalovirus serostatus, patient age, disease type, disease stage, Karnofsky performance score, patient ancestry, patient-donor allele mismatching at HLA-DRB1 or HLA-DQB1, and time from diagnosis to transplantation and stratified by graft type and year of transplantation; the transplantation-related mortality model was adjusted for patient-donor cytomegalovirus serostatus, patient age, disease type, disease stage, graft-versus-host disease prophylaxis, Karnofsky performance score, patient ancestry, patient-donor allele mismatching at HLA-DRB1 or -DQB1, T-cell depletion, and time from diagnosis to transplantation and stratified by graft type and year of transplantation. Abbreviation: HR, hazard ratio.

†Previously reported by Petersdorf et al.
‡Only 10 rs429916AA patients in cohort 2; therefore, AA and AC genotype patients were combined.
DOA alleles are negatively associated (Data Supplement). Finally, we characterized HLA-DOA in HLA homozygous reference cells (Data Supplement). The reference cells KAS116 and COX were homozygous DOA*01:01:05 and rs429916AA. Taken together, these data strongly support rs429916A as a marker for HLA-DOA*01:01:05.

DOA*01:01:05 and Mortality

We tested the hypothesis that DOA*01:01:05 affects outcome. Increasing numbers of DOA*01:01:05 alleles were associated with higher risks of mortality and transplantation-related mortality, even after adjusting for HLA mismatching (Table 2).

The silent substitutions that define HLA-DOA*01:01:05 to 01:01:06 occur at sites that putatively influence methylation. We observed that HLA-DOA expression values for DOA*01:01:05-homozygous patients are consistent with mean expression among DOA*01:01:05-negative patients (Data Supplement). In summary, DOA*01:01:05 and rs429916A define a haplotype, but neither are causative of mortality. We hypothesized that the true susceptibility gene is carried on DOA*01:01:05- and rs429916A-positive haplotypes.
We leveraged the strong long-range LD between rs429916 and variants within the class II region to identify the causal gene (Fig 2). Because HLA-DO and -DM interact to modulate antigen presentation,12-15 we defined HLA-DOB, -DMA, and -DMB in HLA homozygous reference cells. Together with published data16 no specific HLA-DOB-, -DMA, or -DMB alleles are linked exclusively with DOA*01:01:05, which suggests that variation at these loci cannot explain mortality risk (Data Supplement). Three striking features were found for HLA-DRB1. First, HLA-DRB1 alleles differed according to zero, one, and two DOA*01:01:05 alleles, notably DRB1*03:02 (0.2%, 5.4%, and 28.6%, respectively) and DRB1*15:03 (0.5%, 3.1%, and 21.4%, respectively); in contrast, DRB1*15:01 was negatively correlated (12.3%, 24.1%, and 7.1%, respectively; Data Supplement). Second, DRB1*03:02 and DRB1*15:03 were only observed among nonwhite patients, whereas DRB1*03:01 and DRB1*15:01 were found in multiple ancestries: DRB1*03:01 (white American) versus DRB1*03:02 (African American; P = 1.3E-57) and DRB1*15:01 (white American) versus DRB1*15:03 (African American; P = 5.2E-114; Data Supplement). Among the 28 haplotypes represented in the 14 DOA*01:01:05-homozygous patients, 15 (54%) carried DRB1*03:02 and/or DRB1*15:03. The 14 patients were African American (n = 10), white American (n = 3), and Hispanic American (n = 1). In sharp contrast, DOA*01:01:05-negative patients encoded DRB1*03:01 and/or DRB1*15:01. These results indicate that DRB1 alleles were skewed across the entire study population and that two alleles, DRB1*03:02 and DRB1*15:03, were enriched among DOA*01:01:05-rs429916A-positive patients.

HLA nomenclature provides information on the HLA-DRB1 allele sequence (structure), which defines the constituent amino acid residues that influence peptides accommodated by the HLA-DRB groove (function; Fig 3). The third striking feature was the strong LD between HLA-DRB1 residues 26/28/30 and DOA*01:01:05 (Data Supplement). DRB1*15:01 encodes FDY, DRB1*15:03 FDH, and DRB1*03:02 FEY. The frequency of FEY and FDH increased with zero, one, and two DOA*01:01:05 alleles, whereas FDY was inversely proportional. Formal LD analysis (Data Supplement) demonstrates the strongest LD association between FEY and DOA*01:01:05 (P < 10E-15) followed by FDH (P < 10E-15); FDY has the strongest negative LD (P < 10E-15). Furthermore, rs429916A is in positive LD with FDH (P < 10E-15) and FEY (P = 3.3E-12) and in negative LD with FDY (P < 1.0E-12; Data Supplement). Finally, the estimated three-locus haplotype frequency of FEY-DOA*01:01:05-rs429916A in the fine-mapping cohort (0.00146) is greater than the expected frequency on the basis of the product of the three allele frequencies (0.000354), which supports a > 400-kb-long haplotype. In summary, rs429916A-positive patients encode different HLA-HRβ residues than rs429916A-negative patients. Evaluation of residues shared among distinct HLA-DRB1 alleles may shed light on common features that are biologically important in transplantation survivorship.

### HLA-DRB1 and Mortality

In the fine-mapping cohort, we tested the hypothesis that mortality depends on the presence of specific amino acid substitutions in the peptide-binding region of HLA-DRB. The FEY, FDY, and FDH motifs at residues 26/28/30 of HLA-DRB were evaluated because of their strong positive (FEY and FDH) and negative (FDY) LD with rs429916A and HLA-DOA*01:01:05, the proxies for mortality. We hypothesized that presence of FEY and FDH increases the risk of mortality, whereas FDY is protective. With patients...
without FEY, those with FEY had a significantly increased risk of mortality; risks also were increased among patients with FDH compared with those without the motif (Table 2). Compared with patients without FDY, those with FDY had a significantly lower risk of mortality, which suggests a protective effect of the motif. Little evidence was found of a statistical interaction between FEY and FDH ($P = .94$), FEY and FDY ($P = .44$), or FDH and FDY ($P = .75$), which suggests that the effects of one motif did not vary according to the presence of another motif and vice versa. Furthermore, no evidence was found of an interaction between motifs and ancestry ($P = .58$ for FEY; $P = .34$ for FDH; $P = .44$ for FDY), which suggests that the effect of each motif on the risk of mortality was approximately the same across ancestries. In summary, FEY, FDH, and FDY are each candidate determinants worthy of validation.

To validate which, if any, of the three motifs is a marker for mortality, we tested FEY, FDH, and FDY separately in an independent cohort of 3,061 patients (cohort 3; Data Supplement). A similar step-up of mortality hazard was observed for the presence of FEY compared with the absence of FEY (HR, 1.29); however, no protective effect of FDY (HR, 1.08) or at-risk effect of FDH (HR, 0.96) was observed (Table 2). In summary, HLA-DRB1 alleles that encode the FEY motif at residues 26/28/30 of HLA-DRB1 in patients increase the risk of mortality after HLA-mismatched unrelated donor transplantation.

HLA-DRB1 alleles that encode the FEY motif are found at strikingly different frequencies across diverse ancestries ($P = .44$ for FDY), which suggests that the effects of one motif did not vary according to the presence of another motif and vice versa. Furthermore, no evidence was found of an interaction between motifs and ancestry ($P = .58$ for FEY; $P = .34$ for FDH; $P = .44$ for FDY), which suggests that the effect of each motif on the risk of mortality was approximately the same across ancestries. In summary, FEY, FDH, and FDY are each candidate determinants worthy of validation.

To validate which, if any, of the three motifs is a marker for mortality, we tested FEY, FDH, and FDY separately in an independent cohort of 3,061 patients (cohort 3; Data Supplement). A similar step-up of mortality hazard was observed for the presence of FEY compared with the absence of FEY (HR, 1.29); however, no protective effect of FDY (HR, 1.08) or at-risk effect of FDH (HR, 0.96) was observed (Table 2). In summary, HLA-DRB1 alleles that encode the FEY motif at residues 26/28/30 of HLA-DRB1 in patients increase the risk of mortality after HLA-mismatched unrelated donor transplantation.

HLA-DRB1 alleles that encode the FEY motif are found at strikingly different frequencies across diverse ancestries ($P = .44$ for FDY), which suggests that the effects of one motif did not vary according to the presence of another motif and vice versa. Furthermore, no evidence was found of an interaction between motifs and ancestry ($P = .58$ for FEY; $P = .34$ for FDH; $P = .44$ for FDY), which suggests that the effect of each motif on the risk of mortality was approximately the same across ancestries. In summary, FEY, FDH, and FDY are each candidate determinants worthy of validation.

To validate which, if any, of the three motifs is a marker for mortality, we tested FEY, FDH, and FDY separately in an independent cohort of 3,061 patients (cohort 3; Data Supplement). A similar step-up of mortality hazard was observed for the presence of FEY compared with the absence of FEY (HR, 1.29); however, no protective effect of FDY (HR, 1.08) or at-risk effect of FDH (HR, 0.96) was observed (Table 2). In summary, HLA-DRB1 alleles that encode the FEY motif at residues 26/28/30 of HLA-DRB1 in patients increase the risk of mortality after HLA-mismatched unrelated donor transplantation.

HLA-DRB1 alleles that encode the FEY motif are found at strikingly different frequencies across diverse ancestries ($P = .44$ for FDY), which suggests that the effects of one motif did not vary according to the presence of another motif and vice versa. Furthermore, no evidence was found of an interaction between motifs and ancestry ($P = .58$ for FEY; $P = .34$ for FDH; $P = .44$ for FDY), which suggests that the effect of each motif on the risk of mortality was approximately the same across ancestries. In summary, FEY, FDH, and FDY are each candidate determinants worthy of validation.

To validate which, if any, of the three motifs is a marker for mortality, we tested FEY, FDH, and FDY separately in an independent cohort of 3,061 patients (cohort 3; Data Supplement). A similar step-up of mortality hazard was observed for the presence of FEY compared with the absence of FEY (HR, 1.29); however, no protective effect of FDY (HR, 1.08) or at-risk effect of FDH (HR, 0.96) was observed (Table 2). In summary, HLA-DRB1 alleles that encode the FEY motif at residues 26/28/30 of HLA-DRB1 in patients increase the risk of mortality after HLA-mismatched unrelated donor transplantation.

HLA-DRB1 alleles that encode the FEY motif are found at strikingly different frequencies across diverse ancestries ($P = .44$ for FDY), which suggests that the effects of one motif did not vary according to the presence of another motif and vice versa. Furthermore, no evidence was found of an interaction between motifs and ancestry ($P = .58$ for FEY; $P = .34$ for FDH; $P = .44$ for FDY), which suggests that the effect of each motif on the risk of mortality was approximately the same across ancestries. In summary, FEY, FDH, and FDY are each candidate determinants worthy of validation.

To validate which, if any, of the three motifs is a marker for mortality, we tested FEY, FDH, and FDY separately in an independent cohort of 3,061 patients (cohort 3; Data Supplement). A similar step-up of mortality hazard was observed for the presence of FEY compared with the absence of FEY (HR, 1.29); however, no protective effect of FDY (HR, 1.08) or at-risk effect of FDH (HR, 0.96) was observed (Table 2). In summary, HLA-DRB1 alleles that encode the FEY motif at residues 26/28/30 of HLA-DRB1 in patients increase the risk of mortality after HLA-mismatched unrelated donor transplantation.

HLA-DRB1 alleles that encode the FEY motif are found at strikingly different frequencies across diverse ancestries ($P = .44$ for FDY), which suggests that the effects of one motif did not vary according to the presence of another motif and vice versa. Furthermore, no evidence was found of an interaction between motifs and ancestry ($P = .58$ for FEY; $P = .34$ for FDH; $P = .44$ for FDY), which suggests that the effect of each motif on the risk of mortality was approximately the same across ancestries. In summary, FEY, FDH, and FDY are each candidate determinants worthy of validation.

To validate which, if any, of the three motifs is a marker for mortality, we tested FEY, FDH, and FDY separately in an independent cohort of 3,061 patients (cohort 3; Data Supplement). A similar step-up of mortality hazard was observed for the presence of FEY compared with the absence of FEY (HR, 1.29); however, no protective effect of FDY (HR, 1.08) or at-risk effect of FDH (HR, 0.96) was observed (Table 2). In summary, HLA-DRB1 alleles that encode the FEY motif at residues 26/28/30 of HLA-DRB1 in patients increase the risk of mortality after HLA-mismatched unrelated donor transplantation.
Transplantation is optimal when the benefits of curative therapy outweigh the risks associated with the procedure itself. The current data suggest that knowledge of patients’ HLA-DRB residues may supplement prognostication measures of transplantation outcomes to enhance counseling,34 may guide clinical decision making about the optimal timing of transplantation and tailored selection of drugs and regimens,1 and may enable high-risk patients to benefit from increased surveillance of post-transplantation complications. The current study sheds light on a role for the patient’s germline HLA haplotype in outcome after unrelated donor transplantation. Future studies of the importance of DRB residues in haploidentical and cord blood transplantation will further understanding of the HLA barrier in transplantation for these modalities. Knowledge of patients with high-risk HLA-DRB residues has utility in the design of future clinical trials35 and in the interpretation of health outcomes data.4,36 In these ways, the patient’s unique genetic make-up can be leveraged to improve his or her survival.

### Table 3. Effect of the HLA-DRB1 FEY Motif According to Ancestry

<table>
<thead>
<tr>
<th>Ancestry</th>
<th>Group</th>
<th>No.</th>
<th>Mortality HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American (n = 412)</td>
<td>No FEY</td>
<td>342</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any FEY</td>
<td>70</td>
<td>1.60 (1.18 to 2.17)</td>
<td>.002</td>
</tr>
<tr>
<td>Hispanic American (n = 582)</td>
<td>No FEY</td>
<td>506</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any FEY</td>
<td>76</td>
<td>1.35 (0.99 to 1.84)</td>
<td>.060</td>
</tr>
<tr>
<td>White American (n = 5,036)</td>
<td>No FEY</td>
<td>5,021</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any FEY</td>
<td>15</td>
<td>1.27 (0.70 to 2.30)</td>
<td>.430</td>
</tr>
</tbody>
</table>

**NOTE.** To address whether mortality was solely due to the increased fraction of Hispanic and African Americans who possess FEY motifs relative to whites, we evaluated the effect of FEY among patients of African, Hispanic, and white ancestry in cohorts 1, 2, and 3 combined. The models adjusted for year of transplantation; use of total body irradiation; age; cytomegalovirus serostatus; disease risk; graft type; HLA-A, -B, -C, -DRB1, -DQB1, -DPB1 mismatch; and donor age. Two Asian Americans in cohorts 1, 2, and 3 encoded HLA-DRB1 alleles with the FEY motif and were not analyzed.

Abbreviation: HR, hazard ratio.

Disclosures provided by the authors are available with this article at jco.org.

### AUTHOR CONTRIBUTIONS

Conception and design: Effie W. Petersdorf, Mary M. Horowitz
Collection and assembly of data: Effie W. Petersdorf, Mari Malkki, Stephen R. Spellman, Michael D. Haagenson
Data analysis and interpretation: Effie W. Petersdorf, Philip Stevenson, Mari Malkki, Roland K. Strong, Mary M. Horowitz, Ted Gooley, Tao Wang
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors
HLA Germline in Transplantation

REFERENCES

16. The IPD-IMGT/HLA Database: Welcome to IPD-IMGT/HLA. https://www.ebi.ac.uk/ipd/imgt/hla
17. University of California, Santa Cruz: UCSC Genome Browser. https://genome.ucsc.edu
20. RCSB Protein Data Bank: 4FOX: Crystal structure of HLA-DM bound to HLA-DR1. http://www.rcsb.org/pdb/explore/explore.do?structureId=4FOX
22. RCSB Protein Data Bank: 4X5W: HLA-DR1 with CLIP102-120M107WV. http://www.rcsb.org/pdb/explore/explore.do?structureId=4X5W

Affiliations

Effie W. Petersdorf, University of Washington; Fred Hutchinson Cancer Research Center; Philip Stevenson, Malikki, Roland K. Strong, Ted Gooley, Fred Hutchinson Cancer Research Center, Seattle, WA; Stephen R. Spellman, Michael D. Haagenson, Center for International Blood and Marrow Transplant Research, Minneapolis, MN; and Mary M. Horowitz, Tao Wang, Center for International Blood and Marrow Transplant Research and Medical College of Wisconsin, Milwaukee, WI.

Support

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Patient HLA Germline Variation and Transplant Survivorship

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Effie W. Petersdorf
No relationship to disclose

Philip Stevenson
No relationship to disclose

Mari Malkki
No relationship to disclose

Roland K. Strong
Stock or Other Ownership: Cocrystal Pharma
Consulting or Advisory Role: Cocrystal Pharma
Research Funding: Denali Therapeutics, AvidBiotics, Aduro Biotech, Ono Pharmaceutical
Patents, Royalties, Other Intellectual Property: Fred Hutchinson Cancer Research Center

Stephen R. Spellman
Travel, Accommodations, Expenses: Astellas Pharma

Michael D. Haagenson
No relationship to disclose

Mary M. Horowitz
Research Funding: BioVitrum, Otsuka, Novartis, Therakos, Telomere Diagnostics, Gamida Cell, Kite Pharma

Ted Gooley
Stock or Other Ownership: Johnson & Johnson
Consulting or Advisory Role: Nohla Therapeutics, Agensys, Pharmacyclics
Travel, Accommodations, Expenses: Kiadis Pharma

Tao Wang
No relationship to disclose
Acknowledgment

We thank Mark Gatterman and Dawn Moran for their outstanding technical assistance and Gary Schoch and Chris Davis for database support.