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8/8 and 10/10 High-Resolution Match Rate for the Be The Match Unrelated Donor Registry

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ABSTRACT

The National Marrow Donor Program's Be The Match Registry® facilitates the worldwide utilization of unrelated donor (URD) grafts for patients in need of a hematopoietic cell transplantation. In this study, we estimate the URD match rate for patients of White (WH), Hispanic (HIS), Asian/Pacific Islander (API), and African American/Black (AFA) race and ethnic groups. We chose 1344 URD at random as "pseudo-patients" (PP) to estimate the likelihood of finding an 8/8 or 10/10 high-resolution HLA-A,-B,-C,-DRB1 (and -DQB1) matched URD. Searches were conducted in the Be The Match Registry database for each PP at 2 time points: 2009 and 2012. URD who were a potential match for a PP by low/intermediate resolution were HLA typed by sequence-based typing to resolve the matching status. The 8/8 match rate for WH PP improved from 68% in 2009 to 72% in 2012. Corresponding match rates were 41% to 44% for HIS, 44% to 46% for API, and 27% to 30% for AFA, for 2009 and 2012, respectively. The 2012 10/10 match rates were 67% for WH, 38% for HIS, 41% for API, and 23% for AFA. These results provide baseline 8/8 and 10/10 match rate estimates by race for patients seeking an URD.

INTRODUCTION

Allogeneic hematopoietic cell transplantation is a therapy for malignant and nonmalignant blood disorders. The National Marrow Donor Program's (NMDP) Be The Match Registry® has facilitated over 61,000 unrelated donor (URD) transplantations since its inception in 1987. Human leukocyte antigen (HLA) matching between the URD and the patient is important for transplantation success, reducing treatment-related mortality and graft-versus-host disease, and improving overall survival [1-4]. High-resolution (HR) matching at 4 loci (8 alleles) HLA-A, -B, -C, and -DRB1 provides superior outcomes compared with transplantations having 1 or more mismatches [2]. Although transplantation is performed on behalf of individuals of all race and ethnic (hereafter "race") groups, disparities exist in the percentage of patients achieving transplantation with a suitable URD, as well as in the quality of HLA match of those URD available to the patient [5,6].

Previous studies have estimated the HLA match rate of patients based on modeling simulations using population genetics frequencies [7-10]. Although modeling approaches are statistically sound, they rely on a number of simplifying assumptions and approximations. Furthermore, the clinical goal for HLA matching (4 loci, HR) is higher than the majority of the URD typing in the registry (3 loci, intermediate resolution). Although patients registering through the NMDP would seem like a logical cohort to study, selection bias confounds the group because of patient access of care, insurance barriers, referral patterns, and socioeconomic factors. In addition, resources of time and money often prevent complete typing of all potential 8/8 URD matches on actual patient searches before moving forward with a 7/8 or lesser match. Therefore, we ran mock URD searches on randomly selected donors listed on the Be The Match Registry serving as "pseudo-patients" (PP) to avoid these potential sources of

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bias. Combined with centralized URD selection and HLA typing, this approach provided a better controlled estimate of the actual likelihood of finding a matched URD than clinical searches.

This study estimates the 8/8 HLA-A, -B, -C, and -DRB1 and 10/10 (with HLA-DQB1) HR match rate for patients from the 4 most populous US race categories—White (WH), Hispanic (HIS), Asian/Pacific Islander (API), and African American/Black (AFA) [11]. Historically, in NMDP patient populations, AFA have the lowest proportion of 8/8 HLA-matched transplantations, whereas WH have the highest.

In the practice of URD selection, transplantation centers navigate the process of selecting URD while balancing protocols and treatment of the patient's disease. Although centers look for adult URD who match at 8/8, and often 10/10, alternatives to this include 7/8 mismatched URD and umbilical cord blood transplantations [12]. Knowledge of the 8/8 match rate of various populations can help patients and transplantation centers understand the likelihood and typical experience of search outcomes to facilitate a conversation with patients about the search strategy and potential for alternative treatment options early in the process should no fully HLA-matched available donor be found.

METHODS

PP Population

Previous randomly selected NMDP volunteers, registered as potential URDs on the Be The Match Registry, were typed at HR HLA-A, -B, -C, -DRB1, and -DQB1. Selection of the non-WH URD populations (ie, HIS, API, AFA) and HLA typing were previously reported [13], and a more recent set of random WH URD were typed using a similar process (NMDP unpublished data). URD race is self-reported at the time of donor registration into the registry. This random group of URD presented a cohort of HLA genotypes that were sampled and used as PP to run URD searches using a static NMDP registry file from January 2009 that contained 6 million HLA-A, -B, -DRB1–typed URD with a composition of 68% WH, 10% HIS, 7% API, 8% AFA, and 6% reported as unknown, declined, other, or multiple race. URD typed at only HLA-A and -B (ie, no HLA-DRB1) on the registry were not included in this study.

The initial PP URD search yields 1 of 3 outcomes: (1) 8/8 HR URD match identified, (2) no possibility of an 8/8 HR URD, or (3) URD has potential to match at 8/8 but further typing is required. PP cases in outcome category 3 were accrued until 200 were studied in each race group resulting in total populations (categories 1 to 3 combined) of WH = 377, HIS = 307, API = 270, and AFA = 390.

PP search results were computed using the HapLogic matching algorithm and viewed in the NMDPs internal SearchLink software. A second phase of the project using a static NMDP registry file from January 2012 updated the same PP cases for changes in the 8/8 match rate and to establish a 10/10 match rate. The 2012 file represents 3 years of URD file growth (~43% increase) to a total file size of 8.6 million HLA-A, -B, -DRB1–typed URD. The institutional review board of the NMDP approved this study.

HR Match Definition

PP with at least 1 potential 8/8 match were evaluated for identification of URDs meeting the definition of HR match. HR match was defined as any of the following: (1) an allele match, (2) an allele match within the exons encoding the antigen recognition site, or (3) an allele match when restricting to genotypes containing alleles on the common and well-documented HLA allele list [14].

HLA Typing

An NMDP HLA specialist evaluated each search, ranked potential 8/8 URD in order of likelihood of match, and identified per locus typing required to achieve the HR match definition. URD samples were typed in order of rank for each PP, until an HLA match was found, no further potential match existed, or only URDs without an available sample for typing remained (referred to as "indeterminate" in post-HLA–typed PP). The majority of URD typed for this study were from NMDP donor centers, including the US C.W. Bill Young Department of Defense Marrow Donor Program, and the German and US DKMS donor centers. The German DKMS donor center obtained new samples from willing URD when a stored sample was not accessible. Several other URD registries also participated, including the Caitlin Raymond International Registry (United States), Europdonor Foundation (Netherlands), Gift of Life Bone Marrow Foundation (United States), Hadassah Bone Marrow Donor Registry (Israel), Knochenmarkspenderzentrale Dusseldorf (Germany), and The Tobias Registry (Sweden).

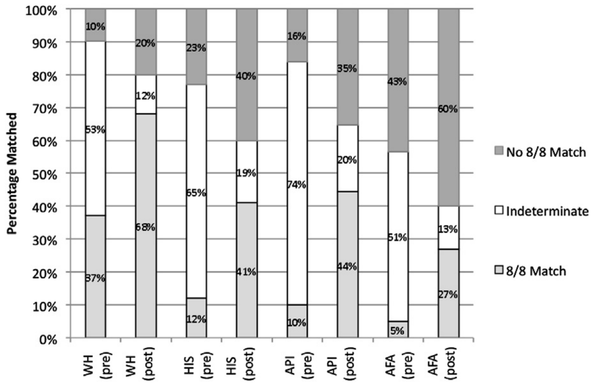

Figure 1. 2009 registry. Pre (initial search results) and post (after donor HLA typing) typing 8/8 HR match rate by race. Indeterminate in "pre" typing columns is defined as PP with potential URD to match at 8/8 but further typing is required. Indeterminate in "post" typing columns is defined as PP without a defined 8/8 match and additional URD remain untested. WH indicates White; HIS, Hispanic; API, Asian/Pacific Islander; AFA, African American/Black.

NMDP and URD samples from the other participating registries, excluding the German DKMS, were typed by HR sequence-based typing techniques at HistoGenetics, LLC. German DKMS samples were typed at the DKMS Life Science Lab using sequence-based typing. Both laboratories are American Society for Histocompatibility and Immunogenetics–accredited and URD typing included blind quality control samples to ensure accuracy of typing and reporting.

Statistical Analysis

Univariate logistic regression testing the association of race group on the likelihood of finding an 8/8-matched URD (post-HLA typing activities) was performed. P values of $< .05$ were used to determine statistical significance. The dependent variable included the binary categories 8/8 HR match and no 8/8 HR match. *No 8/8 HR match* was defined as all searches where no 8/8 URD was found plus indeterminate cases (ie, only URD without testable samples remained).

RESULTS

Figure 1 shows the 2009 8/8 HR match rate in a side-by-side view for each race group, before and after donor typing. This depicts the experience of the PP at initial URD search results and the outcome after HLA typing of potentially matching URD. The post-typing 8/8 URD match rate for WH was 68%; HIS, 41%; API, 44%; and AFA, 27%. All race groups demonstrated a dramatic increase in match rate based on the HLA typing of URD to achieve the HR match definition.

Figure 2A to D displays the experience of URD HLA typing and match outcome by PP race using the year 2009 registry. Eighty-seven percent of WH PP who identified an 8/8 match via URD HLA typing (n = 118) required 2 or fewer URD selections (median, 1; range, 1 to 132), contrasted with PP who did not identify a HR match after URD typing (n = 82; median 3; range, 1 to 298). Ninety-eight percent of HIS PP where a match was found via HLA typing (n = 91) required 2 or fewer selections to identify an 8/8 match (median, 1; range, 1 to 74) versus PP who did not identify a match (n = 109; median, 3; range, 1 to 85), 91% of API PP (n = 95) required 2 or fewer selections (median, 1; range, 1 to 61) versus (n = 105; median, 3; range, 1 to 140), and 99% of AFA PP (n = 84) required 2 or fewer selections (median, 1; range, 1 to 5) versus (n = 114; median, 1; range, 1 to 61), respectively.

The second phase of the project, which looked at the 8/8 match rate of this same cohort of PP based on the 2012