HLA-DPB1 permissive mismatches enables the identification of optimally HLA-matched donors without unrealistic donor registry sizes

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Overview

The current selection practice in hematopoietic stem cell transplantation (HSCT) for an unrelated donor includes matching of HLA-A, -B, -C, -DRB1, and -DQB1 at high typing resolution defined by the respective antigen recognition domain (ARD). Several publications suggest additional consideration of the locus HLA-DPB1 in donor selection to improve clinical outcome [1,2]. In contrast to the first 5 loci, a donor with beneficial HLA-DBP1 genotype is not chosen by matching the ARD but by shared T-cell epitopes (TCE) in otherwise mismatched HLA-DPB1 alleles.
Here, we investigated to which extent the inclusion of HLA-DPB1 to the donor profile requires stem cell donor registries to recruit additional donors to sustain current matching probabilities when permissive mismatches are applied in the selection practice.

Method

In September 2011, DKMS Germany added HLA-DPB1 to the typing profile of all newly recruited donors. Based on a sample of n=250,000 donors of self-assigned German ethnic background with high resolution typing by NGS, we estimated six-locus haplotype frequencies using Hapl-o-Mat, our implementation of the EM-algorithm [3]. Using these haplotype frequencies, we calculated matching probabilities for a German donor in a registry of German donors by application of TCE group matching for HLA-DPB1. For comparison, we also computed matching probabilities based on 8/8, 10/10 and 12/12 high-resolution matching.

Results

The relative difference in numbers of registered donors to maintain a given matching probability is considerably smaller between a 8/8 matching paradigm and a 10/10 paradigm than between 10/10 and 12/12.

Adding HLA-DPB1 to the 10/10 donor selection profile while maintaining a matching probability of e.g. 70% approximately requires a sixfold higher number of donors in a donor registry if allele matching is required similar to the other 5 HLA loci.

However, if permissive mismatches for HLA-DPB1 are considered, less than a twofold higher number of donors is necessary.

Matching probabilities

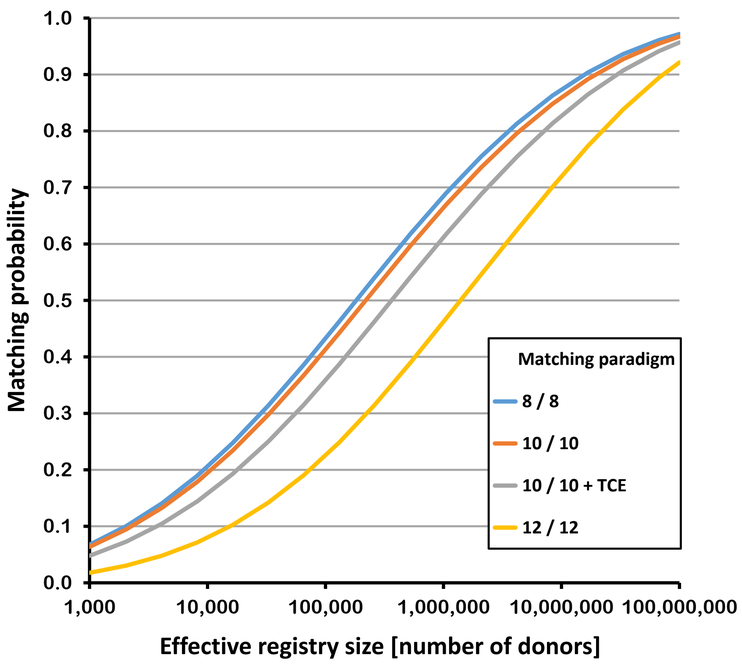

Figure 1 Probability to find a suitable German donor for a German patient considering different matching paradigms.

Matching probabilities				
Registry size	8 / 8	10 / 10	10 / 10 + TCE Match	12 / 12
10^3	5.8 %	5.5 %	4.8 %	1.5 %
10^4	19.1 %	18.1 %	15.8 %	7.2 %
10^5	42.3 %	40.9 %	35.9 %	20.9 %
10^6	69.4 %	67.4 %	61.2 %	44.0 %
10^7	90.0 %	87.6 %	82.8 %	70.0 %
10^8	98.1 %	97.8 %	95.7 %	91.3 %

Registry sizes				
Matching-probability	8 / 8	10 / 10	10 / 10 + TCE Match	12 / 12
0.3	29,000	37,000	56,000	225,000
0.4	75,000	90,000	150,000	575,000
0.5	180,000	220,000	360,000	1,400,000
0.6	450,000	550,000	900,000	3,400,000
0.7	1,200,000	1,500,000	2,400,000	8,400,000
0.8	3,600,000	4,400,000	7,200,000	22,200,000

Conclusions

The addition of HLA-DPB1 to the donor recruitment typing and the application of TCE group matching allows donor registries to maintain a high matching probability with considerably fewer donors as would be required by high-resolution matching using a 12/12 paradigm.

References

[1] Zino E. et al., *AT-cell epitope encoded by a subset of HLA-DPB1 alleles determines nonpermissive mismatches for hematologic stem cell transplantation*, Blood, 2004, 103, 4, 1417

[2] Crivello P. et al., *The Impact of Amino Acid Variability on Alloreactivity Defines a Functional Distance Predictive of Permissive HLA-DPB1 Mismatches in Hematopoietic Stem Cell Transplantation*, BBMT, 2015, 233-241

[3] Schäfer C., Schmidt A. H., Sauter J., *Hapl-o-Mat: Open-Source Software for HLA Haplotype Frequency Estimation from Ambiguous and Heterogeneous Data*, BMC Bioinformatics, 2017, 18:284

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