HLA-DPB1 and DPA1~DPB1 linkage mismatch affects the survival of recipients receiving HLA-14/14 matched unrelated donor HSCT

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Aim

The present study aimed to analyze the clinical impact of DPA1 and DPB1 mismatches in recipients undergoing unrelated donor HSCT matched at the HLA-A, B, C, DRB1, DQB1, DQA1, and DRB3/4/5 loci (HLA-14/14 matched) , to screen for mismatch types with different risk stratification at the level of the HLA-DPB1 allelic and the HLA-DPA1~DPB1 linkage mismatch level in the Chinese population.

Methods

we collected 258 recipients with hematological disease who underwent HLA-10/10 matched URD-HSCT. HLA-A, -B, -C, -DRB1, -DQB1, -DRB3/4/5, -DQA1, -DPA1, and -DPB1 typing was performed for the donors and recipients using hybrid capture-based next-generation sequencing (NGS) technology. After excluding 8 cases with DQA1 or DRB3/4/5 mismatches, we included 250 cases with HLA-14/14 matching for further analysis. For the first time, we established the DPA1~DPB1 linkage mismatch analysis approach in the international arena to analyzed the effect of both DPA1 and DPB1 mismatches on HSCT. The primary outcomes for 2-year overall survival (OS), disease free survival (DFS), non-relapse mortality (NRM), and II-IV acute graft-versus-host disease (aGVHD) were analyzed by the univariable and multivariable analysis.

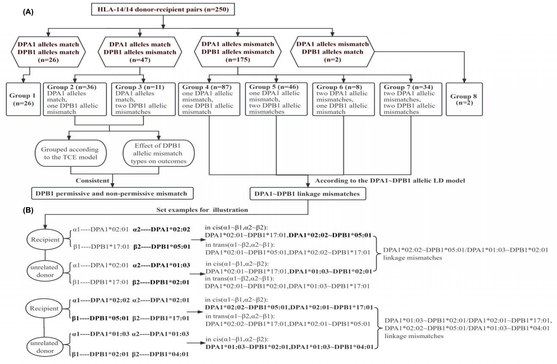

FIGURE 1 **Process flowchart for the analysis of HLA-DPA1 and HLA-DPB1 allelic matches and mismatches between donor-recipient pairs.** (A) All HLA-14/14 donor-recipient pairs were grouped by HLA-DPA1 and HLA-DPB1 allelic match and mismatch numbers. DPB1 allelic mismatch types were classified according to the TCE model and the effects on outcomes when DPA1 alleles matched; analysis approach for linkage mismatches determined through standard LD values of DPA1 DPB1 allelic linkage. (B) Selecting the most common DPA1 DPB1 linkage mismatch types to illustrate the arrangement of one and two linkage mismatches.

Results

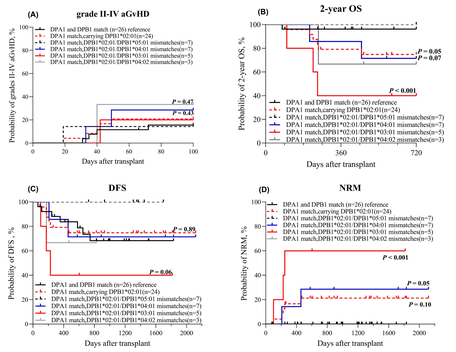

FIGURE 2 **DPB1*02:01/DPB1*03:01 mismatches affect grade II–IV aGvHD, OS, DFS and NRM rates in comparison with DPA1 and DPB1 match.** (A) There were no significant differences in grade II–IV aGvHD. (B) DPB1*02:01/DPB1*03:01 mismatches significantly decreased 2-year OS rates. (C) DPB1*02:01/DPB1*03:01 mismatches decreased DFS rates (p = 0.06). (D) DPB1*02:01/DPB1*03:01 and DPB1*02:01/DPB1*04:01 mismatches significantly increased NRM.

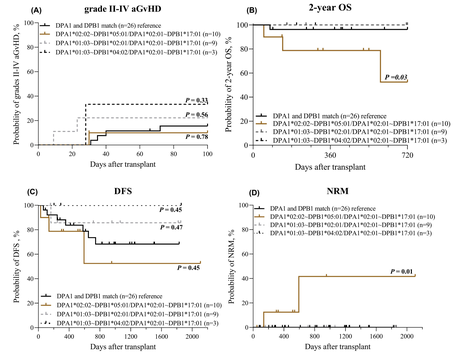

FIGURE 3 **The impact of DPA1*02:01~DPB1*17:01 and other DPA1~DPB1 linkage mismatches on grade II–IV aGvHD, OS, DFS and NRM rates in comparison with DAP1 and DPB1 matched group.** (A) There were no significant differences in grade II–IV aGvHD. (B) DPA1*02:02~DPB1*05:01/DPA1*02:01~DPB1*17:01 linkage mismatches significantly decreased 2-year OS rates. (C) There were no significant differences in DFS rates. (D) NRM increased significantly with DPA1*02:02~DPB1*05:01/DPA1*02:01~DPB1*17:01 linkage mismatches.

The proportion of matched DPA1 and DPB1 alleles was only 10.4% (26/250). The remaining 89.6% of donors and recipients demonstrated DPA1 or DPB1 mismatch.

In the DPA1 matched and DPB1 mismatched group, accounting for 18.8% (47/250) of the cohort, DPB1*02:01/DPB1*03:01 allelic mismatches were associated with decreased 2-year OS and increased NRM.

DPB1*02:02/DPB1*05:01 and DPB1*02:01/DPB1*05:01 mismatches showed no impact on outcomes. Moreover, the specific allelic mismatches observed were consistent with the DPB1 T-cell epitope (TCE) classification as permissive and non-permissive.

We innovatively established an analysis method for DPA1~DPB1 linkage mismatch for cases with both DPA1 and DPB1 mismatched, accounting for 70% (175/250) of the total. DPA1*02:02~DPB1*05:01/DPA1*02:01~DPB1*17:01 linkage mismatches were associated with lower 2-year OS, especially among AML/MDS recipients. DPA1*02:02~DPB1*05:01/DPA1*01:03~DPB1*02:01 linkage mismatches showed no impact on outcomes.

Results

Given the results of the univariable and multivariable analyses, DPB1*02:02/DPB1*05:01 and DPB1*02:01/DPB1*05:01 allelic mismatches were classified as ‘permissive’, whereas DPB1*02:01/DPB1*03:01 mismatches were classified as ‘non-permissive’, consistent with the TCE model.

DPA1*02:02~DPB1*05:01/DPA1*02:01~DPB1*17:01 linkage mismatches were not recommended when selecting an unrelated donor, particularly for AML/MDS recipients. However, seven types of DPA1 DPB1 linkage mismatches showed no difference in outcomes in comparison with DPA1 and DPB1 match and could be recommended when selecting an unrelated donor.

TABLE 1 **Classification of HLA-DPB1 allelic mismatch types and DPA1~DPB1 linkage mismatch types.**

Classification	HLA-DPB1 allelic mismatch types*
Permissive mismatches	DPB1*02:02/DPB1*05:01
	DPB1*02:01/DPB1*05:01
Non-permissive mismatches	DPB1*02:01/DPB1*03:01
Classification	**DPA1~DPB1 linkage mismatch types**
Recommended	DPA1*02:02~DPB1*05:01/DPA1*01:03~DPB1*02:01
	DPA1*02:02~DPB1*05:01/DPA1*01:03~DPB1*04:01
	DPA1*02:02~DPB1*05:01/DPA1*04:01~DPB1*13:01
	DPA1*02:02~DPB1*05:01/DPA1*01:03~DPB1*03:01
	DPA1*02:02~DPB1*05:01/DPA1*01:03~DPB1*04:02
	DPA1*01:03~DPB1*02:01/DPA1*02:01~DPB1*17:01
	DPA1*01:03~DPB1*04:01/DPA1*02:01~DPB1*14:01
Not recommended	DPA1*02:02~DPB1*05:01/DPA1*02:01~DPB1*17:01

*The classifications are consistent with the TCE model.

Conclusion and Innovations

In conclusion, applying the DPA1~DPB1 linkage mismatch analysis approach can identify different types of mismatches affecting transplant outcomes and provide valuable insight for selecting optimal donors for AML/MDS and ALL recipients.

Innovations:

1) For the first time, we have established the analysis method of DPA1~DPB1 linkage mismatch for analyzing the effect of both DPA1 and DPB1 mismatches.
2) The permissive and non-permissive HLA-DPA1, and HLA-DPB1 allelic and linkage mismatches were investigated in the setting of HLA 14/14 super-matched unrelated donors.
3) Risk stratification of different mismatch types was performed to provide clinical recommendation in selecting HLA-DPA1 and DPB1 mismatched unrelated donors.
4) Notably, this analysis excluded the potential influence of DRB3/4/5 and DQA1. We provide recommendations for donor selection for HLA-DPA1 and -DPB1 mismatched URD-HSCT.