HLA molecular mismatch categories revised and validated using updated HLAMatchmaker software

ETY Wong, R Balshaw, IW Gibson, J Ho, J Shaw, M Karpinski, A Trachtenberg, D Pochinco, A Goldberg, P Birk, M Pinsk, DN Rush, PW Nickerson, C Wiebe

Departments of Medicine, Pathology, Immunology, Pediatrics and Child Health, University of Manitoba, Winnipeg Manitoba, Canada
George and Fay Yee Centre for Healthcare Innovation University of Manitoba, Winnipeg Manitoba, Canada

Background:

HLAMatchmaker is a tool commonly used to quantify donor-recipient HLA molecular mismatch. HLA-DR/DQ molecular mismatch (mMM) categories had been previously published using HLAMatchmaker(v2.2) and validated as a prognostic biomarker of primary alloimmunity in several cohorts. However, HLAMatchmaker has undergone several version changes over the years, the latest being HLAMatchmaker(v3.1), which include an updated repertoire of alleles, revision of eplets – both antibody-verified and theoretical, and, for the first time, the inclusion of interlocus class II (HLA-DR/DQ/DP) eplets. We examined the reproducibility of HLA-DR/DQ mMM categories as prognostic biomarkers for primary alloimmunity using HLAMatchmaker(v3.1).

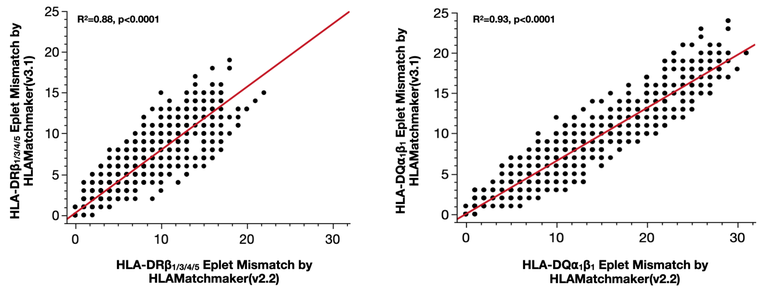
Methods:

We analyzed 949 well-characterized kidney transplant recipients. HLAMatchmaker(v3.1) was used to determine the eplet mismatch for each molecule individually at each HLA-DR and HLA-DQ locus. The single-molecule eplet mismatch (SmMM) threshold for HLA-DR and HLA-DQ was determined by ROC curve analysis correlating SmMM values of individual HLA-DR$\beta_{1/3/4/5}$ and HLA-DQ$\alpha_1\beta_1$ molecules with dnDSA development against these molecules. To develop mMM categories, we determined the maximum SmMM for each recipient at both loci. These values were correlated with any HLA-DR or HLA-DQ dnDSA development for that recipient.

Results:

HLAMatchmaker(v2.2) and HLAMatchmaker(v3.1) resulted in highly correlated SmMM quantification for both HLA-DR$\beta_{1/3/4/5}$ (R_2=0.88) and HLA-DQ$\alpha_1\beta_1$(R_2=0.93, Figure 1). The HLAMatchmaker(v3.1) SmMM threshold was maintained for HLA-DR (Low-risk; maximum HLA-DR$\beta_{1/3/4/5}$ <7), while the thresholds for HLA-DQ were lowered (Low-risk; maximum HLA-DQ$\alpha_1\beta_1$ <6 vs. <9; High-risk; HLA-DQ$\alpha_1\beta_1$ ≥11 vs. ≥15, Table 1A).

Figure 1. Single-molecule eplet mismatch strongly correlated between HLAMatchmaker(v2.2) and HLAMatchmaker(v3.1)



Compared to HLAMatchmaker(v2.2), 768/949 (81%) recipients remained in the same HLA-DR/DQ mMM categories with HLAMatchmaker(v3.1) (Table 1B). No recipient switched from the Low- to High-risk category, or vice-versa.

In a multivariate model, HLAMatchmaker(v3.1) HLA-DR/DQ mMM categories were significant independent correlates of HLA-DR/DQ dnDSA development (Intermediate vs. Low HR 14.3, 95% CI 3.4-60.5, p<0.001; High vs. Intermediate HR 1.8, 95% CI 1.2-2.9,p=0.008; High vs. Low HR 26.4, 95% CI 6.3-109.9, p<0.0001).

These associations remained in a sensitivity analysis excluding recipients with zero HLA-DR/DQ mismatch (n=797, Intermediate vs. Low HR 5.6, 95% CI 1.3-23.7, p=0.02; High vs. Intermediate HR 1.8, 95% CI 1.2-2.9, p=0.008; High vs. Low HR 10.1, 95% CI 2.4-42.5, p=0.002, Table 2).

Table 1A. HLAMatchmaker(v2.2) and HLAMatchmaker(v3.1) HLA-DR/DQ molecular mismatch categories

Risk for Primary Alloimmunity	HLAMatchmaker(v2.2)				HLAMatchmaker(v3.1)			
	Maximum HLA-DRβ$_{1/3/4/5}$		Maximum HLA-DQα$_1$β$_1$	Number of recipients	Maximum HLA-DRβ$_{1/3/4/5}$		Maximum HLA-DQα$_1$β$_1$	Number of recipients
Low	<7	and	<9	227/949 (24%)	<7	and	<6	256/949 (27%)
Intermediate	any	and	9-14	338/949 (36%)	any	and	6-10	369/949 (39%)
High	any	and	≥15	384/949 (40%)	any	and	≥11	324/969 (33%)

Table 1B. Changes in recipients' HLA-DR/DQ molecular mismatch categories between HLAMatchmaker(v2.2) and HLAMatchmaker(v3.1)

HLAMatchmaker(v2.2) HLA-DR/DQ mMM Category	HLAMatchmaker(v3.1) HLA-DR/DQ mMM Category	Number of recipients
Low	Low	209/949 (22%)
Low	Intermediate	18/949 (2%)
Low	High	Nil
Intermediate	Low	47/949 (5%)
Intermediate	Intermediate	263/949 (28%)
Intermediate	High	28/949 (3%)
High	Low	Nil
High	Intermediate	88/949 (9%)
High	High	296/949 (31%)

Table 2. Correlates of HLA-DR/DQ de novo DSA-free survival

	Full Cohort (n=949)		Cohort excluding recpients with zero HLA-DR/DQ mismatch (n=797)	
(n=85 events)	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Male Donor	0.85 (0.53, 1.34)	0.4783	0.85 (0.54, 1.35)	0.5031
Donor Age (per year)	1.00 (0.98, 1.02)	0.8819	1.00 (0.98, 1.01)	0.8301
Deceased Donor	1.27 (0.61, 2.66)	0.5263	1.26 (0.60, 2.63)	0.5460
Previous Transplant	2.66 (0.88, 8.07)	0.0843	2.51 (0.83, 7.62)	0.1029
Panel Reactive Antibody (per %)	0.99 (0.98, 1.00)	0.1527	0.99 (0.98, 1.00)	0.1865
Male Recipient	1.36 (0.85, 2.18)	0.2037	1.36 (0.85, 2.18)	0.1990
Recipient Age (<35 vs. ≥35 years)*	**3.29 (2.04, 5.29)**	**<0.0001**	**3.29 (2.05, 5.29)**	**<0.0001**
Cold Ischemic Time (per hour)	1.02 (0.96, 1.08)	0.6049	1.01 (0.95, 1.08)	0.6558
Delayed Graft Function	0.76 (0.40, 1.44)	0.4007	0.77 (0.41, 1.46)	0.4193
Induction Immunosuppression				
Basiliximab vs. None	0.59 (0.32, 1.09)	0.0908	0.57 (0.31, 1.04)	0.0688
Thymoglobulin vs. None	1.09 (0.60, 2.00)	0.7764	1.07 (0.58, 1.96)	0.8295
Thymogloublin vs. Basiliximab	1.84 (0.88, 3.83)	0.1046	1.88 (0.90, 3.93)	0.0941
Cyclosporine (vs. Tacrolimus)	**2.98 (1.56, 5.69)**	**0.0010**	**3.05 (1.59, 5.86)**	**0.0008**
HLAMatchmaker(v3.1) HLA-DR/DQ mMM Categories				
Intermediate vs. Low	**14.30 (3.38, 60.47)**	**0.0003**	**5.55 (1.30, 23.66)**	**0.0206**
High vs. Intermediate	**1.84 (1.18, 2.88)**	**0.0075**	**1.83 (1.17, 2.86)**	**0.0083**
High vs. Low	**26.36 (6.33, 109.87)**	**<0.0001**	**10.13 (2.41, 42.53)**	**0.0016**

*Previous work demonstrated that recipient age was a non-linear predictor of HLA-DR/DQ dnDSA development, with recipient age <35 years identified as the threshold that best correlated with dnDSA development

Conclusions:

HLA-DR/DQ mMM categories can be reliably reproduced with HLAMatchmaker(v3.1). However, it is important to recognize changes in the SmMM thresholds when using these tools to generate alloimmune risk categories.

Funding Acknowledgements: Canadian Institutes for Health Research I Flynn Family Chair in Renal Transplantation I Paul I Terasaki Research Fund