HLA-DQ Heterodimer Mismatch Number is Associated with De Novo Donor Specific Antibody Development in Pediatric Kidney Transplant Recipients

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Introduction

It has been recognized that structural constraints influence the stability of HLA-DQ α/β trans-heterodimer formation. Stable heterodimers can be formed between α and β chains from the same group: group 1 (DQA1*02/03/04/05/06, DQB1*02/03/04); group 2 (DQA1*01, DQB1*05/06). Recently, the impact of HLA-DQα/β heterodimer mismatch on transplant outcome was investigated in the hematopoietic stem cell transplant setting; however, its role in the solid organ transplant setting has not been elucidated. This study aimed to assess the impact of HLA-DQ heterodimer mismatch number in the HvG direction on de novo DSA (dnDSA) development in a pediatric kidney transplant recipient cohort.

Methods and Materials

Children who underwent kidney transplantation between 1/1/2010 and 3/1/2018 at Stanford Children's Health with ≥12-month follow-up, were included and followed through 9/1/2022. All patients were tested for dnDSA at 0, 1, 2, 3, 6, and 12 months following transplant, at least annually after that, and as clinically indicated.

High-resolution HLA typing was performed on patients and donors using next-generation sequencing. HLAMatchmaker software (HLA DRDQDP Matching v2.2) was used to assess class II eplet mismatches between donors and recipients. Pre- and post-transplant HLA antibody testing was performed with the LABScreen single antigen bead assay (ThermoFisher Scientific). The DQ heterodimer mismatch number was counted based on the possible structurally stable heterodimers formed by the donor that are not present in the recipient.

Primary outcome: HLA-DQ dnDSA. Positive anti-DQ dnDSA was defined as detected with MFI>=3000 in at least two sera post transplant.

Secondary outcomes: Graft failure, adverse graft outcome, proteinuria and biopsy proven rejection. Graft failure was defined as return to dialysis or retransplantation. Biopsies were scored by an expert in pathology per the most recent Banff criteria.

Fisher's exact test was used to compare groups. Survival analysis was performed using the Kaplan Meier method and a violin plot was made.

Results

Of the 288 patients that were considered, a total of 227 met the inclusion criteria. Mean follow-up time was 73 (IQR 96-58) months. The median age at transplant was 14 (IQR 4-17) years, and the majority of the transplant recipients were of Hispanic/Latino origin (39%) and male sex (53%.)

Table 1 shows the baseline patient characteristics. A total of 65 (29%) formed dnDSA against HLA-DQ. Risk of dnDSA formation was analyzed based on the number of heterodimer mismatches. The median heterodimer mismatch number was 2 (IQR 4-2). Fourteen patients were matched with donor DQ alleles.

The risk of dnDSA development was similar among patients with 1-3 DQ heterodimer mismatches but was significantly higher in those with 4 DQ heterodimer mismatches (p=0.007, **Figure 1**)

Table	N = 227
Median age at transplant, years (IQR)	14 (4-17)
Sex n (%)	
Female	106 (47)
Male	121 (53)
Race/Ethnicity, n (%)	
Asian/Pacific Islander	31 (14)
Black or African American	6 (3)
Hispanic/Latino	89 (39)
White	84 (37)
Multiracial	6 (3)
Other	11 (5)
Donor Status, n (%)	
Deceased	171 (75)
Living	56 (25)
Median Heterodimer mismatch number, n (%)	
0	13 (6)
1	43 (19)
2	70 (31)
3	32(14)
4	69 (30)

Table 1. Baseline patient characteristics.

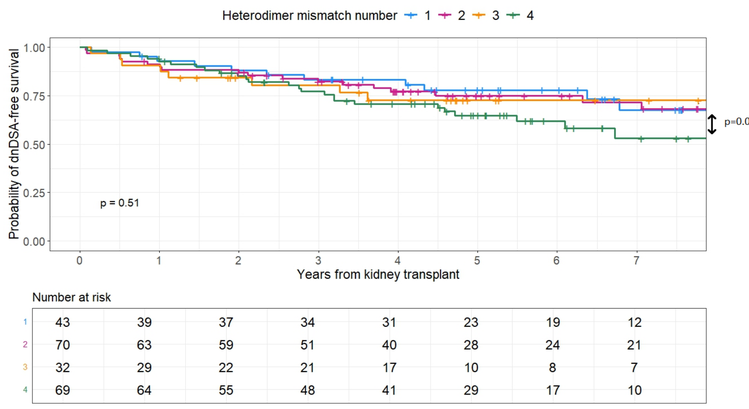

Figure 1. HLA-DQ heterodimer mismatch number and the risk of forming HLA-DQ dnDSA. The patients matched with donor DQ alleles were excluded from the Kaplan Meier analysis.

We investigated the risk of forming HLA-DQ dnDSA in patients with mismatches across G1/G2 DQ groups. Of dnDSA formers, 59% were mismatched between groups vs 54% in non-formers. No statistically significant difference was revealed (p=0.6). Mismatches in G1 or G2 was not shown to be associated with significant higher risk, either.

We compared single molecule eplet mismatch load in HLA-DQ dnDSA formers versus non-formers. The difference between the two groups was not statistically significant (**Figure** 2). Patients who formed HLA-DQ dnDSA had worse graft outcomes compared to those who did not, **Table 2**.

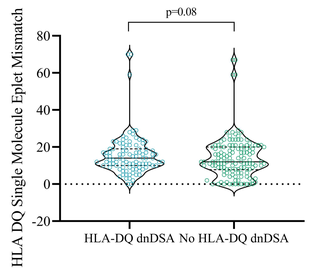

Figure 2: HLA-DQ single molecule eplet mismatch load and the risk of forming HLA-DQ dnDSA

Characteristic	DQ DSA, n= 65	NO DQ DSA, n=162	p value
Age at the time of transplant, yr	13 (16-4)	11 (16-5)	0.5485.
Boys n (%)	33 (51)	88 (54)	0.6607
Living donor kidney transplant, n (%)	14 (22)	42 (26)	0.6097
Follow up time, mo	74 (96-58)	64 (94-51)	0.16758
4 Heterodimer mismatches	27 (37)	42 (26)	0.0256
Heterodimer mismatch number	2 (4-2)	2 (4-1)	0.1096
Graft loss, n (%)	16 (25)	5 (3)	< 0.00001
T-cell mediated rejection	50 (77)	42 (26)	< 0.00001
Antibody mediated rejection	38 (58)	6 (4)	< 0.00001
Adverse graft outcome	(48) 31	(19) 31	0.0001
Proteinuria	8(12)	11(7)	0.1902

Table 2: Comparison of patients that formed HLA-DQ DSA with those that did not (n=227). Adverse graft outcome was defined as estimated glomerular filtration rate dropping below 60 mL/min/1.73m^2

Conclusions and Future Directions

High HLA-DQ heterodimer mismatch number was associated with higher risk of dnDSA formation in children with kidney transplantation. Considering DQ mismatches at the structurally stable heterodimer level may help inform patient risk stratification to improve graft outcomes. Single molecule eplet mismatch load and G1/G2 were not as informative in predicting risk in this cohort of patients.
De novo anti-HLA-DQ antibodies are the most commonly detected DSAs and are associated with lower graft survival compared to all other HLA loci. Better understanding of the pathogenic DQ mismatches may help optimize allocation systems, guide the selection of organs for sensitized patients, and immunologic risk stratification post-transplant to improve graft outcomes.

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