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Association of HLA Molecular Mismatch with Risk and Severity of Rejection in Kidney Transplant Recipients

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Background

Subclinical and clinical acute rejection is associated with poor outcomes in kidney transplant recipients. Current immunosuppressive medications to prevent rejection following transplant increase risk of infections and cancers. Assessment of individual patient risk level is paramount to determine personalized treatment post-transplant.

Traditional Human Leukocyte Antigen (HLA) mismatch evaluates recipient and donor molecules on the serologic level which fail to account for differences and immune system recognition at the molecular level. Considering molecular mismatch may improve rejection risk stratification. Recent studies have examined the role of eplet mismatch load as a marker of alloimmune risk and have demonstrated a significant association between HLA-DQ mismatch and transplant rejection mediated by de novo formation of donor specific HLA antibodies (dnDSAs)[1].

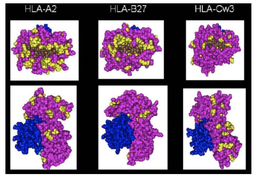

Figure 1. Polymorphic Residues on Class I Antigens[2]

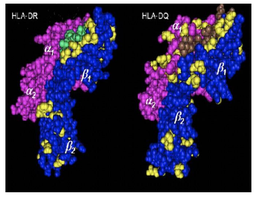

Figure 2. Polymorphic Residues on Class II Antigens[2]

Research Objectives

This project aims to establish the association between molecular HLA mismatch and incidence of acute rejection in the first two years post kidney transplant to improve immunologic risk stratification effectively creating a personalized approach to immunosuppression and immune monitoring post-transplant.

Methods

All donor and recipients that met inclusion criteria underwent HLA molecular genotyping using Next Generation Sequencing. We used the HLA Matchmaker software (DRDQDP Eplet Matching Program V3.1 and ABC Eplet Matching Program V4.0; http://www.epitopes.net) to enumerate eplet mismatches and mismatch load. Calculations were made for total eplet mismatch load and antibody verified mismatch load, as separate calculations for each locus and donor molecule. Subjects were grouped according to occurrence of acute rejection. The TX group had no occurrences of acute rejection, the subAR group had one or more episodes of sub clinical rejection found on protocol biopsy, and the cAR group had one or more episodes of clinical acute rejection, found on indication biopsy. ANOVA test and linear regression was performed to evaluate differences and strengths of association.

References

1. Senev A, Coemans M, Lerut E, et al. Eplet Mismatch Load and De Novo Occurrence of Donor-Specific Anti-HLA Antibodies, Rejection, and Graft Failure after Kidney Transplantation: An Observational Cohort Study. *J Am Soc Nephrol.* 2020:ASN.2020010019.

2. Reneduquesnoy, R. D. (n.d.). What is structurally based HLA matchmaking. HLAMatchmaker. Retrieved October 10, 2022, from http://www.epitopes.net/what.html

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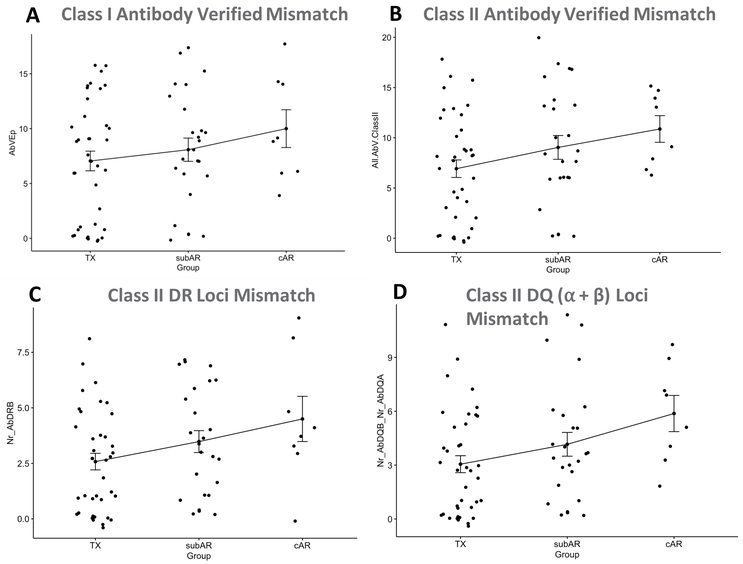
Cohort Characteristics

		CTOT08 cohort		
		cAR (n=8)	subAR only (n=25)	TX (n=38)
Donor Age	Mean	51.0	38.20	42.9
	± SD	13.6	14.28	11.9
	Range	24-67	18-59	20-64
Donor Sex(%)	Male	3(37.5)	9(40.00)	18(47.37)
	Female	8(62.5)	16(60.00)	20(52.63)
Donor Race(%)	White	6(75)	20(80.00)	30(78.95)
	Black or African American	1(12.5)	0(0.0)	4(10.53)
	American Indian or Alaska Native	0(0.0)	0(0.0)	0(0.00)
	Native Hawaiian/Other Pacific Islander	0(0.0)	0(0.0)	0(0.00)
	Asian	1(12.5)	0(0.0)	2(5.26)
	Unknown or not reported	0(0.0)	5(20.00)	2(5.26)
Donor Ethnicity(%)	Not Hispanic or Latino	8(100)	16(64.00)	31(81.58)
	Hispanic or Latino	0(0.0)	7(28.00)	7(18.42)
	Unknown or not reported	0(0.0)	2(8.00)	0(0.00)
Recipients Age	Mean	48.4	46.80	49.7
	± SD	15.3	15.28	15.9
	Range	25-75	21-72	21-75
Recipients Sex(%)	Male	7(87.5)	17(68.00)	22(57.89)
	Female	1(12.5)	8(32.00)	16(42.11)
Recipients Race(%)	White	6(75)	18(72.00)	24(63.16)
	Black or African American	2(25)	1(4.00)	4(10.53)
	American Indian or Alaska Native	0(0.0)	0(0.0)	1(2.63)
	Native Hawaiian/Other Pacific Islander	0(0.0)	0(0.0)	0(0.00)
	Asian	0(0.0)	0(0.0)	4(10.53)
	Unknown or not reported	0(0.0)	5(20.00)	4(10.53)
	More Than One Race	0(0.0)	1(4.00)	1(2.63)
Recipients Ethnicity(%)	Not Hispanic or Latino	8(100)	16(64.00)	30(78.95)
	Hispanic or Latino	0(0.0)	8(32.00)	7(18.42)
	Unknown or not reported	0(0.0)	1(4.00)	1(2.63)
Recipients-Primary reason for ESRD(%)	Cystic (includes PKD)	1(12.5)	2(8.00)	6(15.79)
	Diabetes mellitus	1(12.5)	3(12.00)	7(18.42)
	Glomerulonephritis	2(25)	12(48.00)	14(36.84)
	Hypertension	2(25)	4(16.00)	4(10.53)
	Other	2(25)	4(16.00)	7(18.42)
Recipients-Secondary reason for ESRD(%)	Cystic (includes PKD)	0(0.0)	0(0.0)	0(0.00)
	Diabetes mellitus	0(0.0)	0(0.0)	0(0.00)
	Glomerulonephritis	0(0.0)	2(8.00)	1(2.63)
	Hypertension	1(12.5)	2(8.00)	2(5.26)
	Other	0(0.0)	0(0.0)	2(5.26)
Deceased Donor		0(0.0)	2(8.00)	1(2.63)
Recipient PRA at transplant	PRA class I %(median [IQR])	25[0.00, 2.00]	16.00[10.15,0]	21.05[0,0]
	PRA class II %(median [IQR])	0[0.00,0.00]	16.00[7.05,0]	15.79[0,0]
	PRAcPRA %(median [IQR])	0[0.00,0.00]	28.00[1,52.5]	26.32[6.5,36]
Use of induction therapy	Basiliximab (%)	2(25)	2(8.00)	6(15.79)
	Alemtuzumab (%) (Campath)	6(75)	19(76.00)	20(52.63)
	Antithymocyte globulin (%) (Thymoglobuli)	0(0.0)	4(16.00)	8(21.05)
	Steroid (%)	7(87.5)	22(88.00)	37(97.37)
	IVIG (%)	0(0.0)	0(0.0)	0(0.00)
	Rituximab	0(0.0)	0(0.0)	0(0.00)
Use of desensitization therapy	Received desensitization therapy (%)	0(0.0)	4(16.00)	1(2.63)
Use of maintenance therapy	Steroid (%)	3(37.5)	13(52.00)	16(42.11)
	Tacrolimus (%)	8(100)	25(100.00)	37(97.37)
	Cyclosporine (%)	1(12.5)	0(0.0)	1(2.63)
	Azathioprine	0(0.0)	0(0.0)	0(0.00)
	Mycophenolate (%)	0(0.0)	0(0.0)	0(0.00)
	Sirolimus (%)	0(0.0)	0(0.0)	0(0.00)
	Leflunomide (%)	0(0.0)	0(0.0)	1(2.63)
	Belatacept (%)	0(0.0)	0(0.0)	1(2.63)
	MMF (%)	8(100)	25(100.00)	38(100)
	mTOR (%)	1(12.5)	3(12.00)	2(5.26)
	unknown (%)	0(0.0)	0(0.0)	0(0.00)
Class I All AbV	Mean	10.0	8.1	7.1
	Median	9.0	8.0	7.5
	SD	4.9	5.3	5.5
Class II All AbV	Mean	10.9	9.0	6.9
	Median	11.0	8.0	8.0
	SD	3.8	5.9	5.4
Class II DR	Mean	4.5	3.5	2.6
	Median	4.0	3.0	3.0
	SD	2.9	2.5	2.3
Class II DQ	Mean	5.9	4.2	3.1
	Median	6.0	4.0	3.0
	SD	2.9	3.3	2.9

Table 1. Main demographic, clinical characteristics, and eplet mismatch load of Class I, Class II Antibody verified and DR/DQ loci of study population (n=71).

Results



- Plots of HLA eplet mismatch versus rejection classification by rejection category and HLA Locus. Trend lines show mean +/- SD for each group. Antibody Verified Eplet mismatch number (AbVEp); Transplant Excellence (TX); Subclinical Acute Rejection (subAR); Clinical Acute Rejection (cAR).

Limitations

- Despite a trend in the association of increasing eplet mismatch load and the risk of rejection, the limited cohort size could be the reason for lack of statistically significant results.

Conclusions

- We observed a trend towards higher levels of eplet mismatch associating with greater incidence of both sub clinical and clinical acute rejection (with higher mismatch load associating with more severe, clinical acute rejections). The HLA DQ Loci appeared to have the greatest association with episodes rejection, replicating similar work in the field. Future work will focus on expanding the cohort size to continue to evaluate these relationships. We are also exploring the associations between eplet mismatch load and other immunologic events such as emergence of de novo antibodies and positive screening molecular biomarkers.