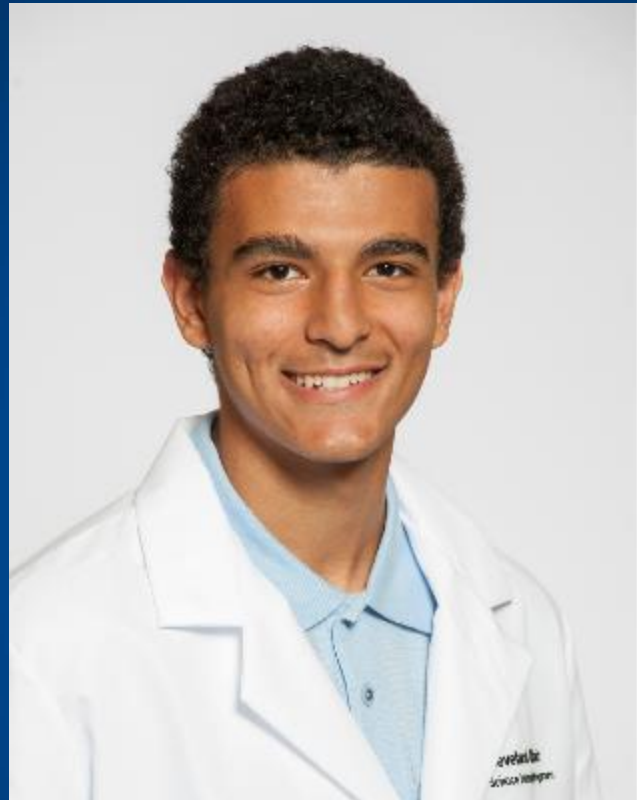


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George Nageeb
Science Internship Program:
Applied Medicine

**Pre-Transplant Panel Reactive
Antibodies and HLA-A*/DQB1*
Mismatches Associated With the
Development of *de novo* Donor
Specific Antibody After Lung
Transplant**

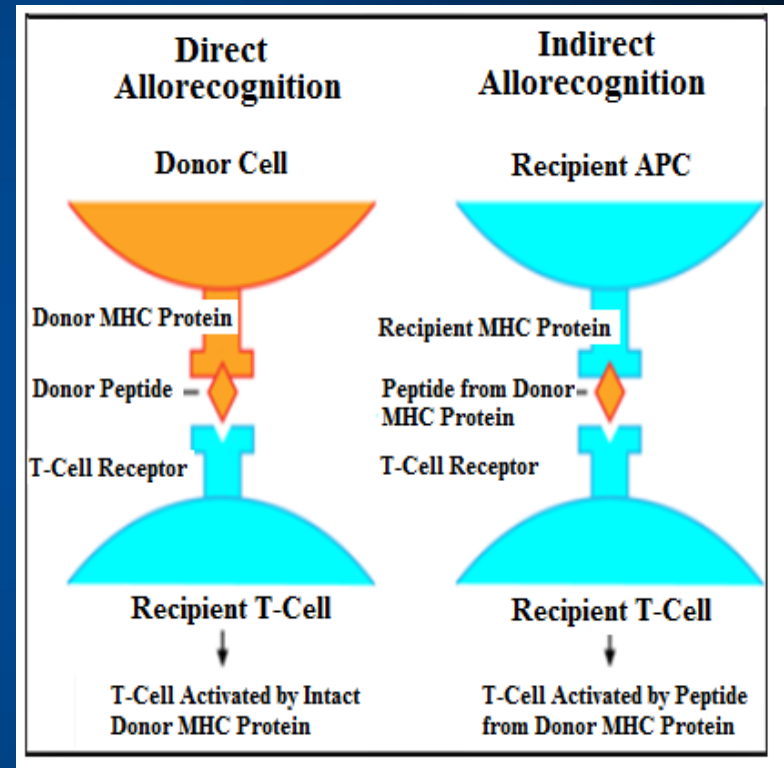
**George Nageeb
Aiwen Zhang, PhD
Elizabeth Winn**

Abstract

- De novo donor specific antibodies (dDSA) cause antibody-mediated rejection in lung transplants.
- We did a retrospective study to explore an association between pre-transplant factors and the appearance of dDSA in 422 patients.
- Our finding is that mismatches in HLA-A* and DQB1* loci, as well as pre-transplant PRA $\geq 30\%$, are significantly associated with dDSA development.

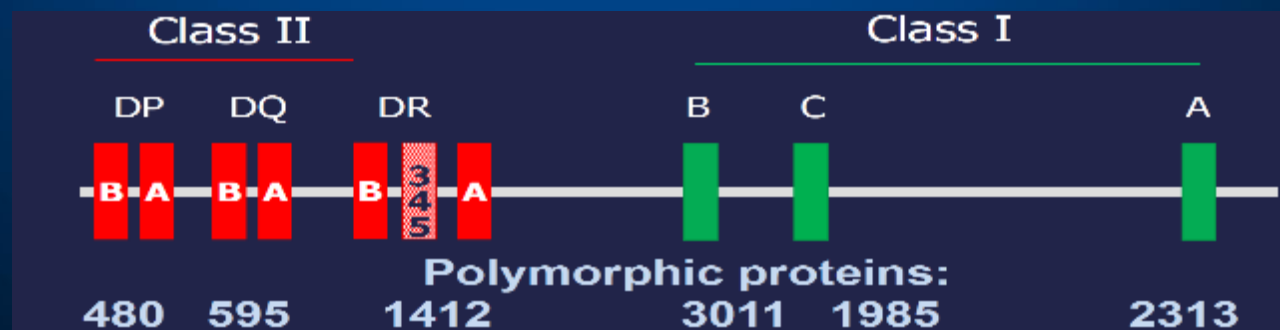
Background

- Major histocompatibility complex (MHC) is a set of cell surface molecules that bind antigens and display them for recognition by T-cells.
- MHC determines the compatibility of donors for organ transplant (Tx).



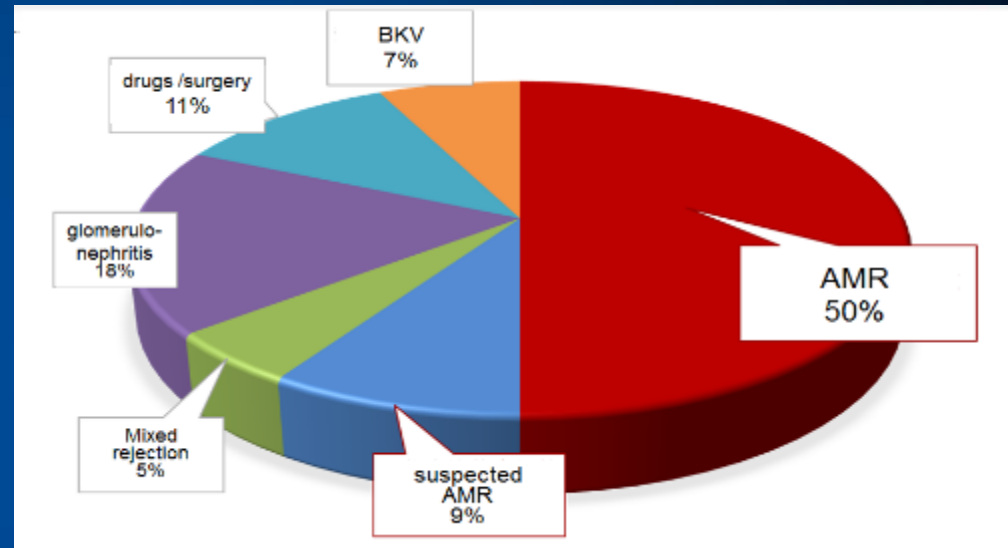
Background

- The human leukocyte antigen (HLA) genes are the human versions of MHC genes that are found in most vertebrates.
- There are 6 different proteins on the cell surface that each have many different forms of allelic gene products.
 - A, B, C, DR, DQ, and DP



Background

- Loss of graft function after Tx = immunological rejection.
- de novo donor specific antibody (dDSA) causes antibody mediated rejection (AMR) of grafts.



Problem/Purpose

- Problem: The incidence of dDSA after lung transplant (LuTx) causes AMR, which is associated with negative Tx outcomes.
- Purpose: We aimed to assess pre-Tx predictors that were associated with the development of dDSA after LuTx.

Hypothesis

- We hypothesized that at least one pre-Tx factor(s) included in this study would be related to the appearance of dDSA.

Methodology

- Retrospective study on 422 patients transplanted between 2012-2016 in CCF.
- Collected data on gender, age, race, blood type, panel reactive antibody (PRA), intensity of dDSA at pre-Tx time, and HLA mismatches.

Data

DSA	Sex	Race	Age	ABO	Pre-Tx cPRA Total	Pre-Tx cPRA Total St	Pre-Tx cPRA CI	Pre-Tx cPRA CI St	Pre-Tx cPRA CII	Pre-Tx cPRA CII St	Pre-Tx MFI Class I	Pre-Tx MFI Class II	A DSA Y or N	# of A mm 0/1/2	B DSA Y or N	# of B mm 0/1/2	C DSA Y or N	# of C mm 0/1/2	DR DSA Y or N	# of DR mm 0/1/2	DQB1 DSA Y or N	# of DQB1 mm 0/1/2
no	F	WHITE	48	O	0	0	0	0	0	0	NA				y	2	y	2	n	2	y	2
no	M	WHITE	64	O	0	0	0	0	0	0			n	na	n	na	n	na	n	na	n	na
yes	F	WHITE	57	A	92	20	91	2	19	19	NA		y	2	y	2	n	2	n	2	n	1
yes	F	WHITE	38	A	0	0	0	0	0	0	NA		y	2	n	2	n	2	n	1	y	1
no	M	WHITE	55	A	0	0	0	0	0	0			n	1	n	2	n	2	n	2	n	2
no	M	WHITE	60	O	22	22	0	0	22	22			n	1	n	2	n	0	n	0	n	0
yes	M	WHITE	66	O	40	0	40	0	0	0	NA		n	2	n	1	n	1	n	2	y	2
yes	M	WHITE	65	O	0	0	0	0	0	0	NA		n	2	n	1	n	1	n	2	y	2
yes	M	WHITE	62	O	0	0	0	0	0	0		G0	n	2	n	2	n	1	n	2	y	2
no	M	WHITE	66	A	23	0	23	0	0	0			n	1	n	1	n	1	n	2	n	1
no	M	WHITE	73	O	22	0	5	3	19	0			n	2	n	2	n	2	y	2	y	2
yes	M	WHITE	66	O	0	0	0	0	0	0		G1	n	2	n	2	n	2	n	2	y	2
yes	M	WHITE	70	O	0	0	0	0	0	0	G1	G1	y	2	n	2	n	2	n	2	y	2
yes	M	WHITE	66	A	0	0	0	0	0	0		G1	n	1	n	2	n	2	y	2	y	2
yes	M	WHITE	73	O	0	0	0	0	0	0	G1	G1	n	2	y	2	n	1	n	2	y	2
no	M	WHITE	51	O	43	0	43	0	0	0			n	0	n	2	n	1	n	2	n	1
yes	M	WHITE	23	A	3	0	3	0	0	0	G1	G0	n	1	y	2	n	2	n	2	y	2
yes	M	WHITE	66	A	13	0	0	0	13	0		G1	n	1	n	2	n	2	n	2	y	2
no	F	WHITE	30	O	0	0	0	0	0	0			n	1	n	2	n	2	n	2	n	2
no	M	WHITE	53	A	0	0	0	0	0	0			n	0	n	1	n	0	n	2	n	2
yes	M	BLACK	63	O	5	0	5	0	0	0	G1		y	2	n	2	n	2	n	2	n	2
no	M	WHITE	75	AB	21	0	21	0	0	0			n	2	n	2	n	2	n	1	n	1
yes	M	WHITE	58	O	0	0	0	0	0	0	G0	G0	n	2	y	1	n	1	n	2	y	2
no	M	WHITE	68	A	0	0	0	0	0	0			n	2	n	1	n	0	n	2	n	1
no	F	WHITE	72	O	0	0	0	0	0	0			n	0	n	2	n	2	n	2	n	2
no	F	WHITE	61	O	17	0	17	0	0	0			n	0	n	2	n	1	n	2	n	1
no	M	WHITE	70	A	0	0	0	0	0	0			n	1	n	2	n	2	n	0	n	0
no	M	WHITE	65	A	0	0	0	0	0	0			n	2	n	1	n	1	n	1	n	1
no	F	WHITE	53	A	0	0	0	0	0	0			n	1	n	2	n	2	n	2	n	1
no	F	WHITE	59	O	0	0	0	0	0	0			n	1	n	2	y	1	n	2	n	2
no	F	WHITE	58	O	0	0	0	0	0	0			n	2	n	2	n	2	n	1	n	0
yes	M	WHITE	67	A	50	0	0	0	50	0		G0	n	2	n	2	n	2	n	2	y	2
no	F	WHITE	21	O	10	2	10	2	0	0			n	0	n	2	n	2	n	2	n	1

*Partial Data. Full data set is available in Allogene Lab database upon request.

Results

- 222/422 (53%) LuTx patients were identified with dDSA.
- Among all loci evaluated, HLA-A was the quickest to appear and HLA-DR was the slowest (Figure 1).

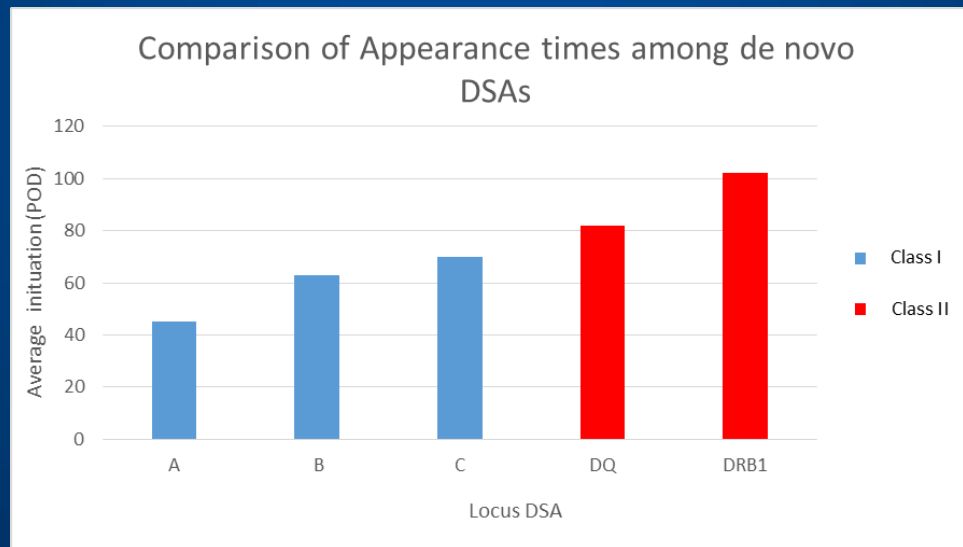


Figure 1. The comparisons of the average post-operation days for dDSA occurrence.

Results

- Among all loci evaluated, HLA-B was the quickest to be resolved and HLA-DQ was the slowest (Figure 2).

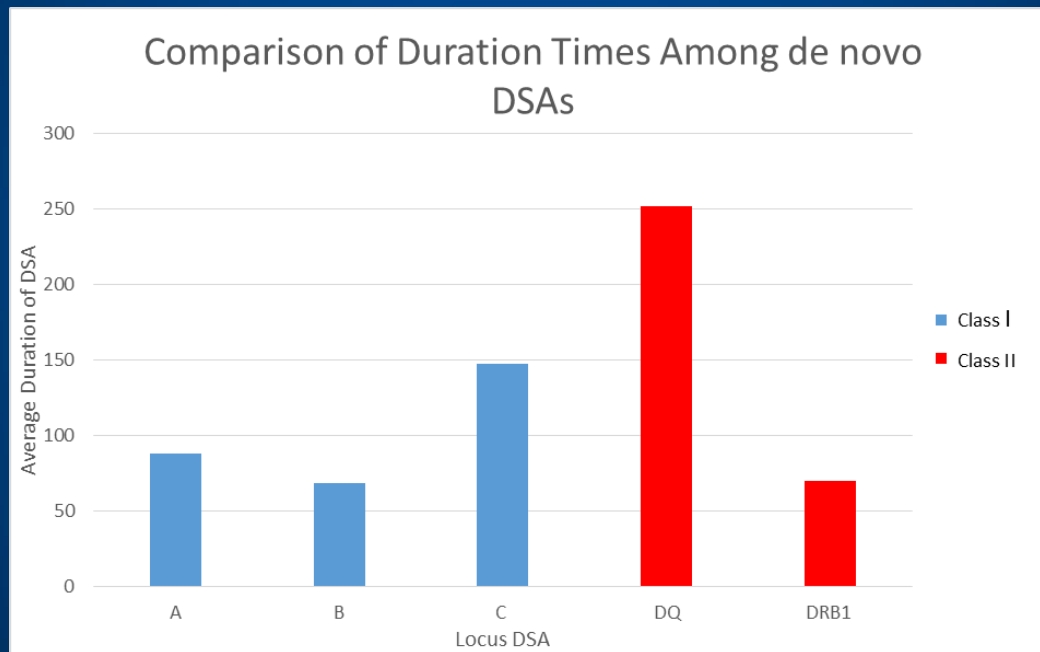


Figure 2. The comparisons of the average post-operation days for dDSA to be resolved.

Results

Table 1. Association of Recipient Demographic Characteristics and Pre-Transplant Histocompatibility Predictors to the Development of De Novo Donor Specific Antibody

	Total (n= 422)	*dDSA Positive (n=222)	dDSA Negative (n=200)	p value
Gender				
Male [n (%)]	300 (71.1)	155 (69.8)	145 (72.5)	
Female [n (%)]	122 (28.9)	67 (30.2)	55 (27.5)	
Race				
Caucasian [n (%)]	376 (89.1)	192 (86.5)	184 (92.0)	
African American [n (%)]	32 (7.6)	20 (9.0)	12 (6.0)	
Others [= (%)]	14 (3.3)	10 (4.5)	4 (2.0)	
Recipient Age				
<40 (n, x±SD of years)	(55, 28±5)	(33, 29±6)	(22, 26±5)	
40-65 (n, x±SD of years)	(218, 57±6)	(119, 56±6)	(99, 57±6)	
>65 (n, x±SD of years)	(149, 69±3)	(70, 69±3)	(79, 70±3)	
				0.053
Pre-transplant Total **PRA ≥ 30% [n (%)]	62 (15.0)	40 (18.4)	22 (11.0)	<0.05
Blood Group (A/B/AB/O)	164/48/19/191	83/24/8/107	81/24/11/84	
***MFI of dDSA at Pre-transplant Class I				
0-500 MFI [n (%)]	387 (91.7)	197 (92.1)	190 (94.1)	
> 500 < 1000 [n (%)]	29 (6.9)	17 (7.9)	12 (5.9)	
Missing [n (%)]	6 (1.4)	NA	NA	
***MFI of dDSA at Pre-transplant Class II				
0-500 MFI [n (%)]	335 (79.3)	179 (81.7)	156 (79.6)	
> 500 < 1000 [n (%)]	80 (19.0)	40 (18.3)	40 (20.4)	
Missing [n (%)]	7 (1.7)	NA	NA	
***HLA Mismatches (0/1/2 MM)				
HLA-A* [Total n (n of 0/1/2 MM)]	412 (9/99/304)	85 (0/5/80)	327 (9/94/224)	<0.001
HLA-B* [Total n (n of 0/1/2 MM)]	419 (1/55/358)	69 (0/5/64)	350 (1/50/294)	
HLA-C* [Total n (n of 0/1/2 MM)]	418 (5/106/305)	38 (1/3/34)	380 (6/103/271)	
HLA-DRB1* [Total n (n of 0/1/2 MM)]	420 (8/69/343)	44 (1/2/41)	376 (7/67/302)	
HLA-DQB1* [Total n (n of 0/1/2 MM)]	418 (23/109/286)	155 (2/6/147)	263 (21/103/139)	<0.001
HLA-DPB1* [Total n (n of 0/1/2 MM)]	242 (167/15/60)	1 (1/0/0)	241 (166/15/60)	

* De novo Donor Specific Antibody

** Panel Reactive Antibody

*** Some individuals missing data for scoring

Conclusions

- Mismatches in HLA-A and HLA-DQ loci were associated with dDSA production after LuTx.
- PRA>30% was associated with dDSA production after LuTx.
- Both of these factors should be considered as risk factors, and warrant closer post-Tx monitoring.

Recommendations

- This is a single center study, and the study results warrant multiple-center study results to further confirm our own.

References

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