First Kidney Allograft Mismatch and Survival in American Indians

A Thesis submitted to the University of Arizona College of Medicine – Phoenix
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Dedication

At the time this document was written, there were 121,384 people waiting to receive a kidney transplant.[1] This research is dedicated to those individuals, with the hope that every kidney transplanted will result in a longer, happier life of its recipient.

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Abstract

Over 121,000 individuals are awaiting renal allograft in the United States.[1] This ongoing imbalance of supply and demand has made research aiming to improve renal allograft survival a necessity. Details of the collection, distribution, and outcomes of renal allografts found in the United Network for Organ Sharing (UNOS) database were used in a retrospective study to identify and evaluate differences in allograft survival between American Indians and other heritage groups. In particular, the study aimed to identify whether American Indians have a similar distribution of HLA mismatches between recipient and donor when compared to other populations; and whether this impacts overall kidney allograft survival. Contingency table and Cox Regression analyses were applied and found that the Hazard Ratio was greater than 1 for all mismatches; and furthermore, an increase in mismatches was proportional to an increase in hazard ratio that was statistically significant. Recipients with 4, 5, or 6 mismatches showed a hazard ratio of 1.466 ($p<0.0564$). The HLA-DR allele has been known historically as the most important locus for transplants.[2] Better matching, particularly at the DR locus, results in improved kidney survival time. Additionally, age, gender, and transplant era were used as major covariates in allograft survival using a proportional hazards model. Increasing age of recipient is associated with increased kidney survival time, and female gender is associated with decreased kidney survival time. Transplant era had a very high Chi-Square of 40.22 and an overall 5% increased survival with most recent transplants living longer than older era transplants. These results have implications for potential policy changes regarding organ allocation in addition to identifying an increased need in organ donation within specific heritage groups.

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Introduction/Significance

There have been over 300,000 kidney transplants performed in the United States since 1988.[1] Continuing research and advances in understanding of the immune system have improved patient prognosis and survival rates. Ongoing research aimed at improving survival of kidney allografts remains a necessity. One important question is the role of kidney recipient heritage in the success or failure of the allograft.[3] Identification of differences between populations and subsequent research of their cause is important for the continued advances in transplant medicine. It is the aim of my thesis to identify the existence of differences in kidney HLA matching and allograft survival between American Indians and other heritage groups. Populations selected for comparison are non-Hispanic Whites, Blacks, Asians, and Hispanics. After first identifying any differences in the HLA mismatch distributions of American Indians and the other heritage groups, I compare the survival time of American Indian kidney allografts in a proportional hazards Cox Regression with age, sex, and transplant era variables as major covariates.

This research has implications for future organ donation and allocation policy. Results of a recent study on HLA matching in an American Indian tribe indicate "small populations with private alleles segregating at the HLA loci pose particular problems for matching donor with recipient from national databases."[2] Private alleles are alleles that found in a single population among a broader collection of populations. If the analysis shows that American Indians with HLA matched donor organs have significant increases in survival compared to those who do not receive matched organs, then it may be wise to encourage the American Indian community to participate in organ donation within their own community. It has been shown that small populations, such as American Indians, commonly encounter difficulties in finding matched organs from outside donors due to private alleles segregating at HLA loci, especially at the HLA-DR locus.[2] However, when these same patients are matched with full heritage Indian donors it is shown that many American Indians recipients would have little to no HLA incompatibility.[2]

If our hypothesis were confirmed that American Indians have shorter kidney allograft survival, and that survival is increased by HLA matching, then it would be wise to establish a

donor community among American Indians. If this community could act amongst itself to provide living-related, living-unrelated, or deceased donor organs for other individuals with the same HLA haplotypes, then allograft survival after transplant would increase. Currently, the United Network for Organ Sharing (UNOS) collects much information including but not limited to ABO type, age, creatinine, CVA, and hypertension when procuring deceased kidneys. Although ethnicity is recorded in the database, no ethnic-directed allocation of deceased donor kidneys is currently in practice. Although ethnic-directed organ allocation may be controversial, if ethnically matched allografts exhibit increased prognosis and survival, it is worth pursuing further in the interest of the patient. Furthermore, an increasing understanding of transplant survival is important for patients to understand, and may encourage more individuals to become organ donors in the interest of posterity.

Research Materials and Methods

The United Network for Organ Sharing (UNOS) data set was utilized for the statistical analysis. All first kidney allograft recipients were identified and selected for further analysis using the NUM_PREV_TX variable. Among first kidney transplant recipients, 2264 were self-described American Indians. Additional populations assessed were non-Hispanic Whites, Blacks, Asians, and Hispanics. The degree of HLA histocompatibility was assessed at the HLA A, B, and DR loci using a matching algorithm. Each locus has two alleles; allowing recipients to receive an overall mismatch score from zero to six. Mismatch data were then compared between American Indians and the populations previously mentioned using contingency tables.

Cox regressions were performed using GTIME_KI as the dependent variable and FAIL_KI as the censoring variable. Age, female gender, and transplant era were covariates. HLAMIS, AMIS, BMIS, and DRMIS were individually evaluated as primary. Finally, a combined HLA 4-6 mismatch category was created and used in an additional regression.

Contingency table analysis and COX regressions were performed by standard methods using SAS software.[4]

Table 1. Explanation of Variables

Variable	Description
AGE	Recipient age (years)
GENDER	Recipient gender. Female = 1, male = 0
ETHCAT*	Recipient Ethnicity Category; 1=White, 2=Black, 4=Hispanic, 5=Asian, 6=American Indian, 7=Pacific Islander, 998=unknown
BMI_RECIP	Recipient BMI at Transplant
CEREB-VASC	Symptomatic Cerebrovascular Disease at Listing (pre 1/1/2007)
DRUGTRT_COPD	COPD
DRUGTRT_HYP	Treated Hypertension (pre 1/1/2007)
ON_DIALYSIS	Most recent candidate on Dialysis (y/n)
NUM_PREV_TX	Number of previous transplants
WORK_INCOME_TRR	Recipient working for income
AGE_DON	Age of donor (years)
GENDER_DON	Donor gender. Female = 1, male =0
ETHCAT_DON	Donor Ethnicity Category; 1=White, 2=Black, 4=Hispanic, 5=Asian, 6=American Indian, 7=Pacific Islander, 998=unknown
BMI_DON_CALC	Calculated Donor BMI
DON_TY	Donor type - deceased, living or foreign
HLAMIS	Total HLA mismatches at A, B, and DR loci. Range from 0-6
AMIS 1	Mismatch at HLA-A1 locus
AMIS 2	Mismatch at HLA-A2 locus
BMIS 1	Mismatch at HLA-B1 locus
BMIS 2	Mismatch at HLA-B2 locus
DRMIS1	Mismatch at HLA-DR1 locus
DRMIS2	Mismatch at HLA-DR2 locus
PTIME	Patient survival time (days)
GTIME_KI	Kidney graft survival time (days)
TX_DATE	Transplant Date
TX_ERA	Transplant era (time in years from first successful kidney transplant to date of patient transplant

*UNOS Ethnicity category referred to as Heritage in this study.

Table 2. Baseline Recipient and Donor Characteristics

Variable (%missing data)	
Donor Characteristics	
Age in years (%; mean ± SD)	36.18 ± 15.37
Female Gender (%; ref. male)	45.25
BMI (%; mean ± SD)	30.47 ± 1143
Heritage (%)	
White	72.87
Black	12.1
Hispanic	11.61
Asian	2.05
American Indian	0.43
Donor Type (%)	
Deceased	67.68
Living	32.29
Foreign	0.02
Recipient Characteristics	
Age in years (%; mean ± SD)	44.72 ± 15.35
Female Gender (%; ref. male)	40.73
BMI (%; mean ± SD)	30 ± 934
Heritage (%)	
White	55.45
Black	25.49
Hispanic	12.62
Asian	4.58
American Indian	0.91
Comorbidities (% with condition)	
Treated HTN (5.13% missing)	76.48
On Dialysis (0.06% missing)	60.91
Symptomatic CVD (5.93% missing)	2.66
COPD (4.44% missing)	1.04

BMI, body mass index; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease

Results

Contingency Tables

Contingency table analysis was performed for the HLAMIS variable for American Indians and the other major heritage groups in the UNOS database.

American Indians versus non-Hispanic Whites, Figure 1. For mismatch categories 0-3 the American Indians had lower percent mismatches than the non-Hispanic whites, while for categories in the higher mismatch group, 4-6, American Indians had higher percent mismatches, with the largest differences in the two greatest mismatch categories, 5, 25.0% American Indian versus 19.9% non-Hispanic white, and mismatch category 6, 12.0% versus 8.9%. When considered by locus, each with 3 mismatch categories, 0, 1, and 2, American Indians had larger percent mismatches in the 2 category when compared to non-Hispanic Whites: A locus, 36.1% versus 33.3%; B locus, 48.7% versus 39.7%; and for HLA-DR, 35.1% versus 27.4%. For each of the 4 contingency tables $p < 0.001$.

American Indians versus non-Hispanic Blacks, Figure 2: In contrast to the matching with non-Hispanic Whites, when compared to non-Hispanic Blacks, American Indians had better matching in lower mismatch categories, 0-3, and also a lower percentage of mismatches in the higher categories, 4-6, than non-Hispanic Blacks. This was also true for the locus by locus comparisons (mismatches 0-2) for category 2 mismatch: A locus, American Indians 36.1% versus non-Hispanic Blacks, 50.9%; B locus, 48.7% versus 57.4%; and DR locus, 35.1% versus 35.9%. For each of the 4 contingency tables $p < 0.001$. This is consistent with findings in previous studies investigating transplant outcomes in Blacks.[5]

American Indians versus non-Hispanic Asians, Figure 3: In each of the better mismatch categories, 0-3, American Indians had higher percentages than non-Hispanic Asians, while in the worse mismatch categories, 4-6 they were represented by lower percentages. For the locus by locus comparisons with 3 mismatch categories 0-2, there was a large difference in the 0 category for all 3 loci: American Indians at the A locus had 20.1% 0 mismatches versus 15.0% for non-Hispanic Asians; B locus, 15.1% versus 8.8%; and HLA-DR, 20.1% versus 14.8%. All 4 contingency tables had p values < 0.001.

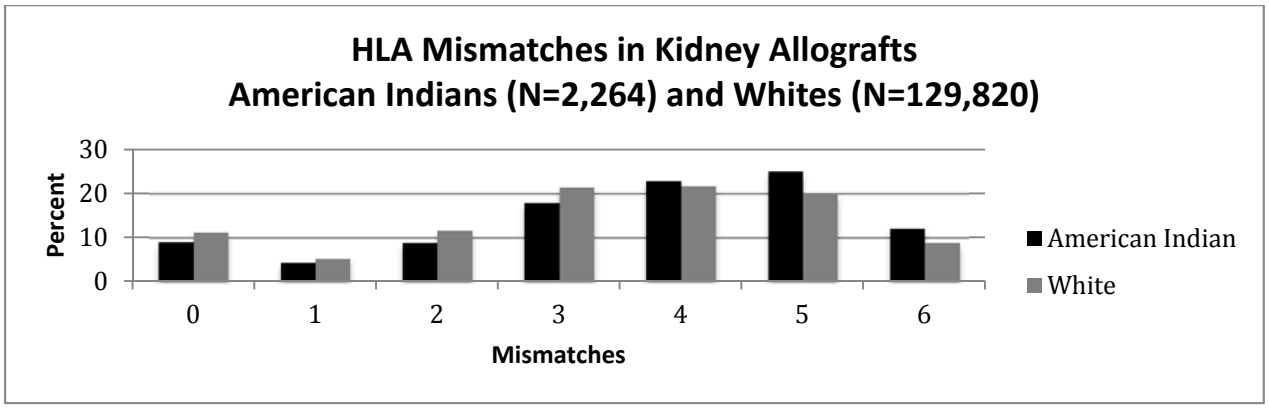
American Indians versus Hispanics, Figure 5: There was no significant difference between the mismatch scores 0-6 in these two heritage groups, p = 0.434. When tested by locus, there was no significant differences in the mismatch scores 0-2 for HLA-A and HLA-B. However, there was a highly significant difference, p < 0.0001, for the HLA-DR locus. American Indians had fewer observations in the better mismatch categories, 0 (20.1% versus 22.1%) and 1 (44.7% versus 47.3%), and more mismatches in the worst category, 2 (35.1% versus 30.6%).

Cox Regressions

A proportional hazard analysis was performed with kidney failure time as the dependent variable and age, gender (reference = male), transplant era, and locus mismatch (reference = 0 mismatch) as explanatory variables (Table 3). In each model age, gender, and transplant era were significantly related to kidney failure time with age and era having significant hazard ratios less than 1.0 and gender, female, being greater than 1.0. There is no significant relation between mismatching for 1 or 2 antigens at HLA-A or HLA-B. For HLA-DR there is a significant relationship between 1 mismatch (HR = 1.366, p = 0.0243) and 2 mismatches (HR = 1.414, p = 0.0177) and the hazard ratios scale with the mismatches, that is, it is larger for category 2 than for category 1. When variable HLAMIS was used as an explanatory variable, with mismatch categories 0-6 (reference = 0 mismatch) none of the mismatch categories 1-6 were significantly related to kidney survival time in American Indians. When mismatches 4-6 were combined in a mismatch category 7, it was marginally related to survival time, p = 0.0564 (Table 3).

Cox regressions were also performed to test the significance of the differences in kidney survival time between American Indians and the other heritage groups in the UNOS data set, while controlling for gender (reference = male), transplant era, variable HLAMIS (reference = 0 mismatch). When American Indians are compared to non-Hispanic whites (reference) the hazard ratio = 1.145 and p = 0.0058. When non-Hispanic Blacks are the reference then HR = 0.647 and p < 0.0001, while for non-Hispanic Asians as the reference, HR = 1.417 and p < 0.0001. Hispanics as reference population had hazard ratios for American Indians not significantly difference from 1.0.

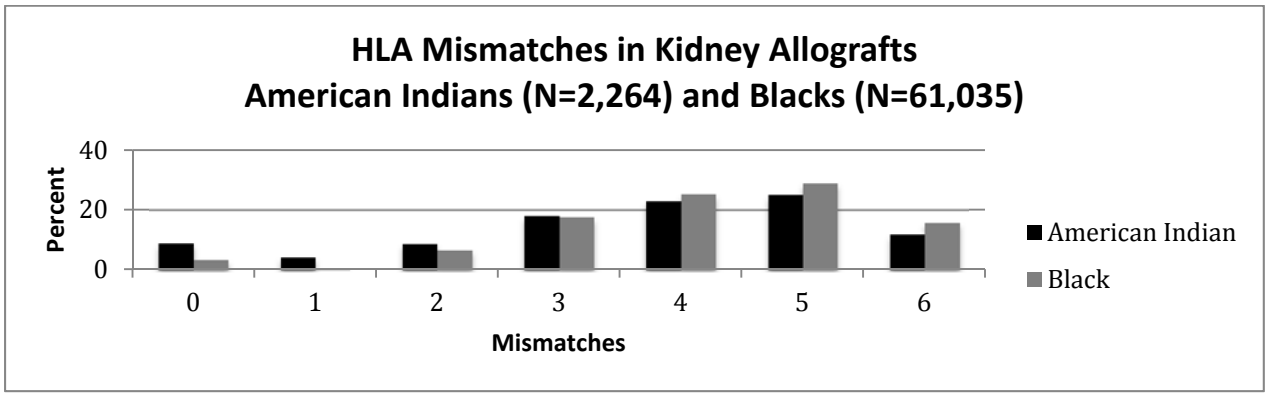
Figure 1. HLA Mismatches in Kidney Allografts – American Indians and Whites.



	Mismatches (%)						
	0	1	2	3	4	5	6
American Indian	9.01	4.28	8.83	17.93	22.88	25.04	12.01
White	11.12	5.23	11.61	21.46	21.75	19.93	8.89

Chi Square 95.19; 6 d.f., p <0.0001

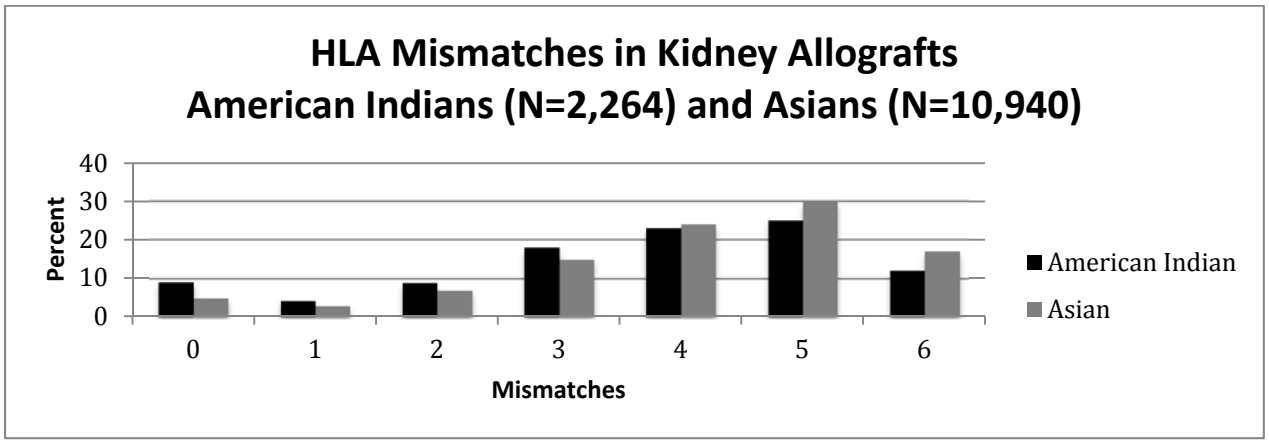
Figure 2. HLA Mismatches in Kidney Allografts – American Indians and Blacks.



	Mismatches (%)						
	0	1	2	3	4	5	6
American Indian	9.01	4.28	8.83	17.93	22.88	25.04	12.01
Black	3.45	2.23	6.66	17.57	25.34	29.03	15.73

Chi-Square 277.42, 6 d.f., p <0.0001

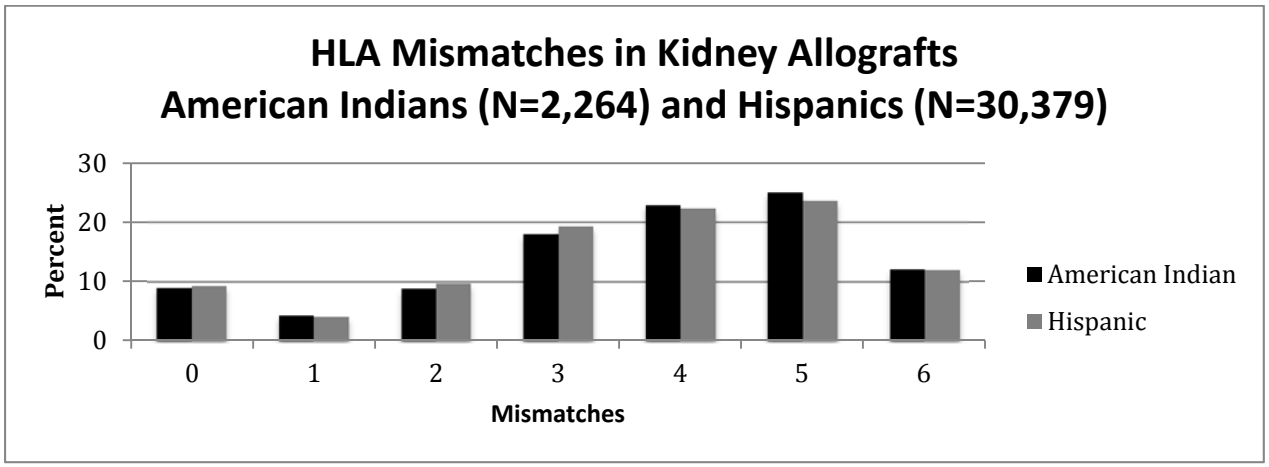
Figure 3. HLA Mismatches in Kidney Allografts – American Indians and Asians.



	Mismatches (%)						
	0	1	2	3	4	5	6
American Indian	9.01	4.28	8.83	17.93	22.88	25.04	12.01
Asian	4.8	2.85	6.96	14.81	23.92	29.76	16.9

Chi-Square 136.89, 6 d.f., $p < 0.0001$

Figure 4. HLA Mismatches in Kidney Allografts – American Indians and Hispanics.



	Mismatches (%)						
	0	1	2	3	4	5	6
American Indian	9.01	4.28	8.83	17.93	22.88	25.04	12.01
Hispanic	9.26	4.08	9.68	19.22	22.28	23.62	11.86

Chi-Square 5.91, 6 d.f., p <0.4335

Table 3. COX regressions. American Indian first Kidney Transplants.

Dependent Variable	
GTIME_KI	Kidney graft survival time (days)
Censoring Variable	
FAIL_KI	Kidney graft failure date
Covariates	
AGE	Age of recipient (years)
GENDER	Female (ref. male)
TX_ERA	Transplant era

COX Models

1. Primary: HLA-A mismatch

Parameter	DF	Chi-Square	Pr>ChiSq	HR
AGE	1	12.19	0.0005	0.989
GENDER	1	4.76	0.0292	1.236
TX_ERA	1	0.01	<0.0001	0.944
AMIS 1 (ref. 0)	1	0.01	0.9053	0.985
AMIS 2 (ref. 0)	1	0.09	0.3482	1.135

2. Primary: HLA-B mismatch

Parameter	DF	Chi-Square	Pr>ChiSq	HR
AGE	1	11.95	0.0005	0.989
GENDER	1	4.72	0.0299	1.234
TX_ERA	1	44.86	<0.0001	0.945
BMIS 1 (ref. 0)	1	0.37	0.5423	1.094
BMIS 2 (ref. 0)	1	1.24	0.2653	1.177

3. Primary: HLA-DR mismatch

Parameter	DF	Chi-Square	Pr>ChiSq	HR
AGE	1	11.23	0.0008	0.989
GENDER	1	4.87	0.0274	1.24
TX_ERA	1	39.84	<0.0001	0.948
DRMIS 1 (ref. 0)	1	5.07	0.0243	1.366
DRMIS 2 (ref. 0)	1	5.63	0.0177	1.414

4. Primary: Total HLA mismatch

Parameter	DF	Chi-Square	Pr>ChiSq	HR
AGE	1	10.71	0.0011	0.99
GENDER	1	5.02	0.025	1.245
TX_ERA	1	40.13	<0.0001	0.947
HLAMIS_MOD1 (ref. 0)	1	0.79	0.3756	1.307
HLAMIS_MOD2 (ref. 0)	1	1.15	0.2839	1.297
HLAMIS_MOD3 (ref. 0)	1	0.73	0.3935	1.207
HLAMIS_MOD7 (ref. 0)	1	3.64	0.0564	1.466

DF, degrees of freedom; HR, hazard ratio; HLAMIS_MOD7, HLA mismatch variables 4-6.

Discussion

Proportional Hazards Analysis

Increasing age of recipient is associated with increased kidney survival. This may be due to diminished immune response to foreign antigens over time. Similar results were found in a previous study by Norman et. al., illustrating that older recipients are "less often sensitized, less likely to experience early rejection episodes, and more often receive lifelong function from their transplanted kidney"[6] than younger organ recipients. Conversely, a study in rats by Wang et. al. found that increased recipient age resulted in increased rates of chronic allograft nephropathy.[7]

Female gender is associated with decreased kidney survival time. This in part due to the inherent differences between men and women's immune responses and increased autoimmunity in females. Furthermore, females are at increased risk for HLA and ABO sensitization due to exposure to fetal HLA antibodies during pregnancy.[8]

Transplant era had a very high Chi-Square of 40.22 and an overall 5% increased survival per year with most recent transplants living longer than older era transplants. This is an encouraging result in that advances in technology, medications, surgical procedures, and organ allocation have resulted in increased survival of transplant recipients.

Cox Regressions

Cox Regressions using total HLA mismatch was used as the explanatory variable result in a Hazard Ratio greater than 1 for all HLA mismatches. The HLAMIS-MOD7 variable (a combination of mismatch categories 4, 5, and 6) also resulted in an increased hazard ratio (1.466) that is statistically significant ($p<0.0564$). Furthermore, an increase in mismatches was proportional to an increase in hazard ratio at all loci.

The HLA-DR allele has been known historically as the most important locus for transplants, and this was confirmed once more in our research as the HLA-DR locus had a hazard ratio greater than one that is statistically significant. Previous studies have shown that full-heritage Pima, and American Indians overall, have a high frequency of the allele DR*1402/6 that is not found in other heritage groups. This allele is absent Europeans, who comprise the largest population of kidney donors.[2]

These results show that poorly matched allografts, particularly at the DR loci, result in

decreased kidney survival.

The policies of organ allocation are continually reviewed and approved by the Secretary of the U.S. Department of Health and Human Services (HHS) prior to becoming federal regulation. Input from the transplant community, public comment process, various committees, and the OPTN/UNOS board of directors are all evaluated prior to developing new policies. The results from this study do support the hypothesis that increased HLA mismatches between recipient and donor decrease allograft survival. This data could be used as evidence to support the importance of HLA matching in organ allocation algorithms.[9]

Future Directions

In the future, ongoing collection and evaluation of kidney allografts by UNOS would supplement this analysis by increasing the sample size of the populations and consequently the power of statistical analysis. Allograft allocation practices and policies may be evaluated in the future to apply this data to reflect the importance of heritage in allograft survival.

On a public health and community outreach level, increased education and awareness of the shortage of organ donation within the American Indian population in particular may foster an environment of increased donation within this group; and potentially increase overall allograft survival in these individuals. The department of Health and Human Services (HHS) conveys a similar idea in it's website, www.organdonor.gov, and states that "although organs are not matched according to race/ethnicity, and people of different races frequently match one another, all individuals waiting for an organ transplant will have a better chance of receiving one if there are large numbers of donors from their racial/ethnic background. This is because compatible blood types and tissue markers—critical qualities for donor/recipient matching—are more likely to be found among members of the same ethnicity. A greater diversity of donors may potentially increase access to transplantation for everyone."[9] In fact, the need is so great among minorities that the HHS has created a National Minority Donor Awareness Week, which lasts from August first through seventh every year for the past 17 years. Although American Indians are included in the minority population, specific outreach and communication within this group could potentially identify barriers to organ donation that exist within our American Indian communities.

Conclusions

Major histocompatibility complex antigens present on donor allogeneic tissue can be recognized by the recipient's immune system. This recognition may result in both cellular and humoral immune responses; and ultimately lead to allograft rejection.[10] American Indians have poorer HLA matching compared to persons of European and Asian heritage. They have similar matching when compared to Hispanic populations, and have slightly higher rates of HLA matching when compared to persons of African heritage. Of the three HLA loci, HLA DR is the most important in terms of kidney survival. This is consistent with what has been found in previous studies. Decreased HLA matching is proportional to kidney allograft survival.

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