Title Page

Title: HLA Loci and Recurrence of Focal Segmental Glomerulosclerosis In Pediatric Kidney Transplantation

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Running Title:
HLA and Nephrotic Syndrome Recurrence

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Commented [AJ1]: Brian –
Please check that all risk HLA are accounted for in all Figures (I made comments)

Importantly—HLA-C3 should include C9 and C10 if we did not already collapse that antigen group??

Minor point—please state "FSGS" Recurrence in the Section headings and Figure Titles for greater clarity...not necessary in text

We hope people will use our Figures in Lectures and important for them to be stand alone!

Commented [BS2R1]: Dr. Jackson, I have responded to all of these below.

Abstract(200 Words):

Recurrent focal segmental glomerulosclerosis (FSGS) after kidney transplantation accounts for the majority of allograft failures in children with primary FSGS. While current research focuses on FSGS pathophysiology, a common etiology for disease and disease relapse remain elusive. HLA proteins are central to adaptive immunity and have been associated with multiple immunologically mediated diseases, including nephrotic syndrome (NS). Given this, we sought to understand the relationship between HLA and recurrent FSGS after transplantation among pediatric patients. We used the Scientific Registry of Transplant Recipient to identify pediatric patients with primary FSGS. We obtained a cohort of patients with a 28% overall disease recurrence rate. HLA DR7, DR53, DQ2, DR52, and DQ7 were associated with increased or decreased risk of recurrent disease after transplantation. We identified a risk haplotype consisting of HLA-DR7, DR53, and DQ2 that was consistently associated with an increased risk of recurrence (OR 1.91 95% CI 1.44-2.54, p<0.001). We also found that donor/recipient concordance for HLA-DQ7 was associated with a decreased risk of recurrence (OR 0.42 95% CI 0.37-0.53, p=0.009). Further study of the relationship of HLA and post-transplant recurrence of FSGS is warranted to better understand mechanism and inform risk assessments and donor selection in this challenging patient population.

Introduction

Post-transplant recurrence of focal segmental glomerulosclerosis (FSGS) occurs in up to 50% of first-time kidney transplant recipients and can be challenging to treat {Fine:2007cd} {Tejani:1992up}. Early post-transplant FSGS recurrence is characterized by nephrotic syndrome (NS) with massive proteinuria within hours to days and progression to acute tubular necrosis, delayed graft function{ 1994.Kim}, and early allograft loss {Baum:2001jo} Post-transplant FSGS recurrence accounts for the majority of allograft failures in children transplanted for primary FSGS {Hariharan:1998dn}. The return to dialysis, sensitization for future transplants, and increased risk of recurrence for subsequent allografts becomes particularly problematic for pediatric recipients {Briganti:2002ba}. Additionally, post-transplant FSGS results in significant recipient morbidity and mortality, places a substantial financial burden on the healthcare system, and contributes to the ongoing organ shortage.

Currently, adequate pre-transplant risk assessment for developing post-transplant FSGS recurrence is lacking and patients have variable responses to therapy following recurrence {Verghese:2018km} {Francis:2018id} {Gonzalez:2011im}. Risk factors for FSGS recurrence have included living donation {Francis:2016hr}{Ding:2014by}{Baum:2004if}, younger age {Ding:2014by} {Nehus:2013hb}, initial steroid sensitivity {Ding:2014by}, white race {Baum:2004if}, and histologic characteristics (mesangial proliferation and minimal change disease) on initial native kidney biopsy and late SRNS {Pelletier:2018kd}. These risk factors, however, have been inconsistent across studies. As we and others and have found associations between HLA class II alleles and recurrence of primary NS, it is plausible that specific HLA may also confer risk of disease recurrence following kidney transplantation{Konrad:1994iy} {Clark:1990it}{Kobayashi:1995ex} {Abe:1995fb} {Kari:2001bf} {Gbadegesin:2015bt}

{Adeyemo:2018cr} {Debiec:2018cn} {Jia:2018fp} {Anonymous:2019ke}. and represent an opportunity to predict post-transplant FSGS risk.

In this analysis, we sought to determine if specific HLA were associated with post-transplant FSGS recurrence in pediatric recipients. We first identified recipient HLA associated with primary FSGS and then explored the relationship of recipient and donor HLA with FSGS recurrence post-transplant.

Methods

Data Source and Study Population

We used data from the Scientific Registry of Transplant Recipients (SRTR). This study was IRB approved and determined exempt (Pro00106450). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US. These data are submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. To enrich our cohort for patients with primary NS, we examined the recurrence rate of patients whose primary indication for transplantation was focal glomerulosclerosis (FSG) or FSGS and included only pediatric patients (age<18). We excluded those with potential secondary causes of FSGS such as diabetes mellitus, congenital anomalies of kidney and urinary tract, and other glomulerulonephritides.

Therefore, all patients who underwent kidney transplant after 1999 (334,947), who were listed by age 18 (15,510), who did not have diabetes (15,344), who were diagnosed with FSG or FSGS (1906), who underwent kidney alone transplant (1901), who were in the follow-up dataset (txf_ki, 1800), were undergoing their first transplant (1718), who had data on recurrence (1530) with at least 6 months of follow-up (1512) and had complete recipient HLA-DR and HLA-DQ information (final N=1196) were included in this analysis.

Primary and Secondary Outcomes

Our primary outcome was recurrence of their primary disease (FSGS). Secondary outcomes examined graft and patient survival time and time to disease recurrence.

Statistical Analyses

Patient and donor characteristics were summarized and compared using chi-squared test for categorical variables and Wilcoxon Rank-Sum tests for continuous variables as appropriate. Univariable logistic regression was performed to determine the association of an HLA antigen (A, B, C, DR51, DR52, DR53, DR, and DQ) with disease recurrence. Of note, generally only serological typing is reported to UNOS. Where molecular data were available, they were converted to serologic types for consistency{ 2018.Kaur}. For all recipient HLA loci except HLA-C, complete data were available for HLA-type. As the association of class I HLA was an exploratory analysis, we performed a complete case analysis for HLA-C associations.

After serial univariable logistic regression across all HLA antigens in the dataset, we tested for significance using the Benajamini-Hochberg method with a false discovery rate of 20%. For all HLA that were significantly correlated at this point, we performed a second set of logistic regression analyses in which we examined the dose effect of these HLA in the recipient's phenotype and the risk of recurrence as well as the dose effect of the donor having a concordant HLA with the recipient. We performed a complete case analysis for both of these dose effect scenarios for each HLA (i.e. we excluded recipients from the concordance analysis if their donor lacked HLA information).

We performed multiple regression to determine our ability to predict post-transplant recurrence. We performed model construction using factors previously postulated to increase the risk of NS recurrence after transplant (age of disease onset, living donor type, race, and ethnicity) as well as all HLA antigen level data (recipient, donor and concordant) that were

significantly correlated with recurrence. We assessed for collinearity by using correlation matrices and evaluation of the variance inflation factor (VIF). We chose our final model by examining the Akaike Information Coefficient(AIC), Bayesian Information Coefficient(BIC), and by examining likelihood ratio tests between models as less significant terms were removed. Receiver operator characteristics for the final models were calculated.

We also performed a time to event analysis for time to recurrence using the Kaplan-Meier method to plot curves and the Log-rank test to compare them.

A sensitivity analysis repeating the initial step of this analysis—performing simple logistic regression to determine the association between recurrence and HLA-antigen—was repeated accounting for race (white vs. non-white) and Latino ethnicity did not substantively change results. All analyses were performed using STATA v. 15 (Statacorp, College Station, TX).

Results

Cohort characteristics and graft failure associated with FSGS recurrence

Patient and donor characteristics are summarized in **Table 1** and **Table 2,** respectively. Patients with post-transplant FSGS recurrence were younger (median age 16 inter-quartile range [9-16] vs. 16 [12-17]), and had lower albumin (Med [IQR] 3.2 [2.3-3.7] vs. 3.7 [3.1-4.2]) and body mass index (MED [IQR] 19.1 [16.8-22.5] vs. 20.3 [17.5-24.8]). Additionally, recurrence was associated with earlier time to graft failure, with median death censored graft survival of 5.4 years in patients with recurrence compared to 13.1 years in patients without recurrence (Logrank p<0.0001, data not shown).

Table 1: Recipient Characteristics

	No Recurrence N=862 (72%)	Recurrence N=334 (28%)	p-value
Gender(F)-n(%)	371 (43%)	146 (44%)	0.83
Age at transplant-Med(IQR)	16.0 (12.0-18.0)	14.0 (10.0-17.0)	<0.001
Age at listing-Med(IQR)	15 (12-17)	13 (9-16)	<0.001
Race-n(%)			0.20
Asian	27 (3%)	5 (1%)	
Black	323 (37%)	115 (34%)	
Multi	11 (1%)	6 (2%)	
Native	5 (1%)	1 (0%)	
Pacific	3 (0%)	4 (1%)	
White	493 (57%)	203 (61%)	
Ethnicity(Latino)-n(%)	251 (29%)	79 (24%)	0.058
Insurance Status			0.40
Public	545 (63%)	208 (62%)	
Private	308 (36%)	125 (37%)	
Self	9 (1%)	1 (0%)	
Time to Dialysis(mos)-Med(IQR)	15 (7-27)	16 (8-29)	0.42
Albumin(g/dL)-Med(IQR)	3.7 (3.2-4.2)	3.3 (2.4-3.8)	<0.001
Body Mass Index (BMI)-Med(IQR)	20.5 (17.5-24.8)	19.3 (17.0-23.0)	0.002

Table 2: Donor Characteristics

	No Recurrence N=862 (72%)	Recurrence N=334 (28%)	p-value
Donor Type(Deceased)-n(%)	645 (75%)	238 (71%)	0.21
Related Donor-n(%)	170 (20%)	74 (22%)	0.35
Donor Gender(F)-n(%)	339 (39%)	139 (42%)	0.47
Donor Age-Med (IQR)	25.0 (19.0-34.0)	26.5 (19.0-38.0)	0.11
Race-n(%)			0.17
Asian	13 (2%)	10 (3%)	
Black	136 (16%)	46 (14%)	
Multi	6 (1%)	0 (0%)	
Native	9 (1%)	1 (0%)	
Pacific	1 (0%)	0 (0%)	
White	697 (81%)	277 (83%)	
Donor Body Mass Index(BMI)-Med (IQR)	25.1 (22.2-28.8)	24.5 (21.4-28.5)	0.088
Cause of Death-n(%)			0.048
Anoxia	138 (21%)	56 (24%)	
CVA	79 (12%)	38 (16%)	
Head Trauma	419 (65%)	137 (58%)	
CNS Tumor	3 (0%)	0 (0%)	
Other	6 (1%)	7 (3%)	
Diabetes-n(%)	5 (1%)	3 (1%)	0.50
Cigarette Smoking-n(%)	64 (10%)	24 (10%)	0.94
Cocaine Use-n(%)	73 (11%)	29 (12%)	0.71
Kidney Cold Ischemia Time(Hours)	10 (5-16)	10 (4-16)	0.70

Recurrence of FSGS after Transplant is predicted by Recipient HLA

We examined the association of HLA antigens with recurrence (Figure 1A). In **Table 3**, we see that HLA antigens HLA-B13, DR7, DQ2, and DR53 were most highly associated with recurrence risk while HLA-C3, B58, DR52, DQ6, and DQ7 were associated with decreased rates of recurrence when controlling for a false discovery rate of 20%. We next assessed a dose effect of these antigens by determining the odds of recurrence given recipient hetero- or

Commented [DECM3]: Figure 1A

Commented [AJ4]: What was the N for HLA-C3 antigen? IT should be low given Labs should be reporting HLA-C3 SPLITS (C9 and C10)
IF we Leave as C3 we should ADD IN C10 and C9

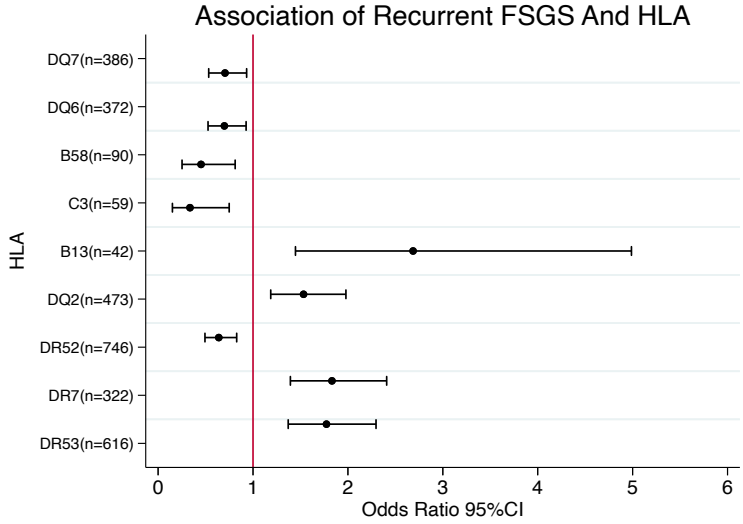
Commented [BS5R4]: I'm hesitant to re-do the whole regression. It would take some time and likely not add that much data. A preliminary look shows that if you collapse C3, 9, and 10 together then there is no association with recurrence. HOWEVER, I just worry about poking the bear too much. I think we can list it as a limitation and just go from there.

Commented [AJ6]: Please explain why you dropped some HLA antigens from the dose analysis---to few number? C3,B13, B58,DR53

Commented [BS7R6]: Don't have homozygosity data on DR51/52/53, just presence or absence. B58 doesn't have enough homozygotes to model. B13 has no homozygotes (note the lower n overall).

homozygosity (Figure 1B). In general, antigens showed a dose response pattern, with homozygosity causing the point estimate to be more extreme in the same direction as the homozygote, though this trend was not observed for DQ7 (**Figure 1B**).

Figure 1a: Association of Recipient HLA antigens with recurrence



Commented [BS8]: Which of these do you want as tables and which as figures? Is table 3 and Figure 1 B the same thing. If so use the figure for both individual and dose response. What do you think Annette

Commented [AJ9R8]: I prefer the figure AND
Of course, prefer the assc first then dose effect second

Figure 1b: Dose response of Recipient HLA Antigens

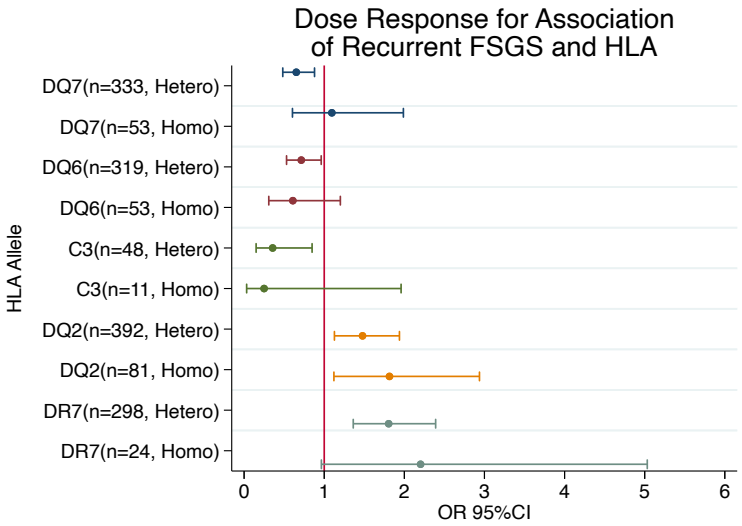


Figure 1 Legend: a) Alleles associated with risk of recurrence after utilizing the Benjamini-Hochberg correction with a false discovery rate of 20%. Odds ratios are for association with disease recurrence. Antigens are ordered by p-value. Point estimates with 95% CI shown. B) Dose response of select Recipient HLA. Heterozygotes and homozygotes for each HLA shown. Odds ratios are for association with disease recurrence. Point estimates with 95% CI shown.

Commented [AJ10]: Can we add N ?
It may help better understand some data like the DQ7

DR7 (N=x, Hetero)

Commented [AJ11]: Can we also include N
B13 (N=X)

Given the diversity of HLA ---statistical analyses are often hindered by low N

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Defining a recipient HLA risk haplotype for FSGS recurrence

Given that HLA-DR7, DR53, and DQ2 represents a common HLA haplotype (**Haplostats reference**) and because we noted that these antigens were positively correlated with one another (**Figure 2**) we interrogated the association of this potential multi-HLA antigen recipient haplotype (now referred to as the risk haplotype) with recurrence. In a simple logistic regression analysis, the risk haplotype increased the risk of recurrence nearly two-fold (OR 1.91 95% CI 1.44-2.54, p<0.001).

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Figure 2: **Correlation between Recipient HLA antigens associated with FSGS Recurrence**

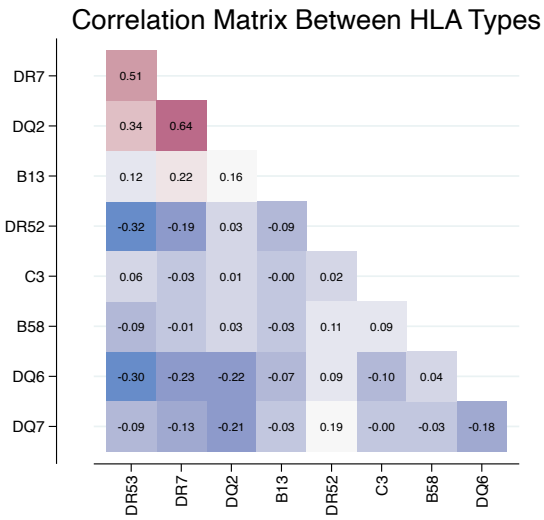

Figure 2 Legend: Association between all Recipient HLA antigens significantly associated with disease recurrence. HLA-DR7, DR53, and DQ2 are all positively correlated with one another.

Recipient HLA Antigens are associated with time to FSGS recurrence

We assessed whether our identified HLA antigens were associated not only with a binary event of recurrence but also time to recurrence. Kaplan Meier plots for each associated

HLA antigen are shown in **Figure 3**. Overall, the results are similar to those shown in **Figure 2**, with a decrease in recurrence free survival for the risk haplotype and B13 and an increase in recurrence free survival for HLA-B58, C3, DR52, DQ6, and DQ7.

Figure 3: Time to recurrence by HLA associated with risk and protection

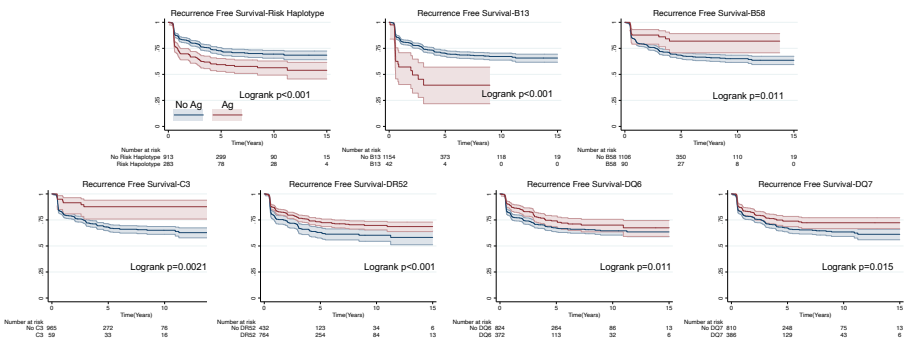

Figure 3 Legend: Kaplan-Meier curves for significantly correlated HLA. Blue curves are without the specified antigen and red curves are with the specified antigen. All comparisons by logrank test.

Impact of donor HLA on FSGS recurrence

We also investigated a role for donor HLA in disease recurrence and potential dose effects when the donor shared a risk or protective HLA antigen with the recipient. The donor HLA alone did not appear to impact recurrence rate; however, there was an apparent dose effect for recipient/donor pairs that shared DQ7. The proportion of patients that recurred was lower in recipient/donor pairs that shared the protective HLA-DQ7 antigen (13.3% for concordance vs. 23.3% for the recipient allele). This effect was confirmed when performing multiple logistic regression using an interaction term between donor and recipient antigens (OR

Commented [BS15]: Will update this to look nicer after your review. Just don't want this to hold us up.

Commented [AJ16R15]: Agree- can we have Y axis labeled and then a simple Legend for each plot delineating the HLA antigen

Also MISSING DR52 from Figure 1

Commented [BS17]: I think that we just get rid of this figure altogether and just let the text stand on its own. It is a little bit confusing to show the statistics of this and I think that bar graph was about the best we can get. Given this, I think we just let this text stand on its own and know that the statistics are correct.

0.42 95% CI 0.37-0.53, p=0.009). Using logistic regression, no other HLA antigens were observed to impact recurrence when shared between recipient and donor.

Using HLA allows for the modest overall prediction of FSGS recurrence

We next constructed a multivariable model for the prediction of disease recurrence. Our initial model included recipient HLA including the risk haplotype (HLA-DR7-DR53-DQ2), HLA-B13, DR52, C3, B58, DQ6, and DQ7 as well as recipient/donor sharing of HLA-DQ7, age at listing, and living related donor status. To account for population structure, we also included non-white race and Latino ethnicity as fixed terms that would not be removed from the model. The initial model was moderately predictive of recurrence (c-statistic 0.68). However, our final model was as predictive (c-statistics 0.68) but had an improve AIC (1098 vs. 1104) and BIC (1142 vs. 1177). The final model included the recipient risk phenotype, B58, C3, DQ6, concordance at DQ7, and age at listing as independent variables.

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Commented [AJ19R18]: Agree- I would keep the text but add simple table
See table format below

Commented [AJ20]: AIC and BIC require definition here or in Methods

	Initial Model	Final Model
	OR/95% CI	OR/95% CI
Race(Black=1)	0.93	0.873
	0.659,1.314	0.623,1.222
Ethnicity(Latino=1)	0.645*	0.654*
	0.442,0.940	0.451,0.948
Risk Haplotype(Recipient)	1.503*	1.718**
	1.053,2.145	1.231,2.397
Risk Haplotype(Donor)	1.229	N/A
	0.850,1.776	
DR52(Recipient)	0.803	N/A
	0.586,1.101	
B13(Recipient)	1.504	
	0.727,3.109	
C3(Recipient)	0.268**	0.270**
	0.111,0.647	0.112,0.650
B58(Recipient)	0.561	0.514*
	0.288,1.092	0.265,0.996
DQ7(Recipient)	0.933	N/A
	0.638,1.364	
DQ7 Match	0.369**	0.334***
	0.198,0.687	0.193,0.577
DQ6(Recipient)	0.656	0.606**
	0.421,1.020	0.430,0.854
DQ6 Match	0.825	N/A
	0.468,1.457	
Age at listing	0.933***	0.931***
	0.901,0.966	0.900,0.964
Living Related Donor	1.249	N/A
	0.856,1.823	
Constant	1.426	1.371
	0.805,2.528	0.819,2.294

* p<0.05, ** p<0.01, *** p<0.001

Discussion

This study represents the first analysis of HLA and FSGS disease recurrence following transplantation in pediatric patients. We demonstrate that certain HLA types are associated with either an increased or decreased risk of recurrence and identify an HLA risk haplotype that encompasses previously defined HLA antigens from NS GWAS analyses. Finally, we show that concordance between donor and recipient HLA may additionally modify recurrence risk.

Multiple teams have sought to better understand the underlying pathophysiology of idiopathic nephrotic syndrome and specifically FSGS. FSGS is defined on biopsy as segmental destruction of the glomerular capillaries and foot process effacement, providing insight into the structural changes that lead to loss of nephron function. However, a full understanding of the environmental, immunologic, and/or genetic triggers that contribute to these destructive changes remain elusive. Familial clustering of FSGS spurred GWAS analyses that revealed a large number of pathogenic gene variants, however, these only account for approximately 30% of SRNS/FSGS cases {Sadowski:2015fk} {Sampson:2016jy}. The majority of genes identified encode for proteins essential to the integrity {Caridi:2001tp} and function of the glomerular podocyte {Akilesh:2011hj}. In contrast, the use of immunosuppressive agents has been shown to slow or mitigate disease progression in numerous cases of FSGS, suggesting an underlying immunological process for many patients {Lieberman:1996tr} {Montane:2003jq}{Tumlin:2006gt}{Duncan:2004cj} {Loeffler:2004et} {Geary:1984ty} {Basu:2015dv}.Experimental and clinical data show improvement of proteinuria after treatment with plasmapheresis, which supports the hypothesis that a circulating factor contributes to podocyte injury {Vecsei:2001jr}. Multiple candidate factors have been identified in blood including urokinase-type plasminogen activator receptor (suPAR), cardiotrophin-like cytokine factor-1 (CLCF-1), anti-CD40 antibodies, and apolipoprotein A-Ib (ApoA-Ib) {LopezHellin:2013dd, Savin:2017hq, Sharma:2015dd, Wei:2015dv, Delville:2014dl}.

HLA disease associations have been documented across numerous primary kidney disorders suggesting an early immunologic etiology for many patients evaluated for transplantation. Indeed, the three HLA identified in our risk phenotype—HLA DR7, DR53, and DQ2—have been previously identified in multiple studies of primary NS {Abe:1995fb, Clark:1990it, Anonymous:2019ke, Konrad:1994iy, Adeyemo:2018cr, Gbadegesin:2015bt, Kobayashi:1995ex, Jia:2018fp}. This may not be surprising given the central role of HLA molecules in initiating adaptive immune responses and their implication in many destructive autoimmune processes. There is evidence that class II HLA polymorphisms have evolved in order to offer maximal protection from pathogens at the expense of potential self-reactivity {Mangalam:2013gg} . In the present study, 4 HLA were associated with increased risk of recurrent FSGS, with 3 being class II HLA, consistent with this theory. Our data, which utilize direct HLA typing (either serological typing or serological equivalents of molecular typing) and not SNP imputation extend the results of previous GWAS {Anonymous:2019ke}{Gbadegesin:2015bt, Adeyemo:2018cr} in a large and diverse cohort. This is important as previous examination of SNP imputation of HLA has found errors, especially in non-white populations{Pappas:2017ix}. Though there have been some small historical studies examining the relationship of serologic HLA type with primary NS and FSGS {GerbaseDeLima:1998gy, Glicklich:1988ev}, we are the first to examine the association of HLA antigens in post-transplant FSGS recurrence.

One unique finding of this study is that HLA concordance between the recipient and kidney donor appeared to influence FSGS recurrence risk. Whereas the conferment of risk appeared to be mediated only by the recipient HLA, the protective effect of HLA DQ7—associated with a decreased risk of recurrence—seemed to be most mediated by concordance with the donor. It is unclear if our inability to find this concordance effect more broadly is due to a true biological difference or meditation at the allelic and not the antigen level. Given there are

conflicting studies on the effect of donor factors in the risk of recurrence {Baum:2004if, Ding:2014by, Nehus:2013hb, Francis:2016hr}, further studies that specifically define HLA alleles based on their genetic sequence would be helpful in answering the clinical question of whether or not HLA concordance—of an allele or haplotype—leads to modifications in the risk of recurrent NS and FSGS.

Although our findings are important, our study has limitations. First, the data is retrospective from a large national registry. Reporting of the clinical event of recurrent FSGS may be incomplete, however, the generally high percentage of patients experiencing recurrence (28%) is compatible with known rates in the literature {Pelletier:2018kd}. Additionally, our dataset does not contain diagnosis codes for other forms of NS such as minimal change disease and therefore we may be excluding some patients inappropriately. The dataset also does not contain data regarding patient histology, known to be important in the clinical course of FSGS. Most importantly, the HLA data are reported from a wide variety of centers and are at the *antigen* level while most genetic studies have found associations of HLA and FSGS at the *allele* level{Jia:2018fp}. This is a major limitation and may be a reason that we did not detect associations between all previously identified HLA with recurrent FSGS. However, our identification of a common risk phenotype DR7-DR53-DQ2 adds credibility to the associations we do find.

In conclusion, we find that certain recipient HLAs are associated with risk of recurrent FSGS in pediatric kidney transplant recipients. Further prospective studies should be undertaken to validate these HLA as risk factors in order to further our understanding of the pathogenesis of FSGS and disease recurrence as well as improve donor selection, and perioperative management for pediatric patients with FSGS.