**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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**Abbreviations**

AIC-Akaike Information Coefficient

BIC-Bayesian Information Coefficient

FSG-Focal Glomerulosclerosis

FSGS-Focal Segmental Glomeruloscelerosis

GWAS-Genome Wide Associatio Studies

NS-Nephrotic Syndrome

OPTN-Organ Procurement and Transplantation Network

SRTR-Scientific Registry of Transplant Recipients

VIF-Variance Inflation Factor

**Abstract**:

**Background**

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 and mechanisms of disease recurrence remain elusive.

**Methods**

We performed a retrospective review of the Scientific Registry of Transplant Recipients (SRTR) to determine the association of specific HLA recurrence of FSGS. Kidney transplants recipients under the age of 19 who were diagnosed with FSGS, who were transplanted after January 1 2000, and who had complete HLA data were included in the study.We performed simple logistic regression on all HLA A, B, C, DR, and DQ represented in the dataset and FSGS recurrence and then determined those associated with recurrence using the Benjamini-Hochberg method for multiple comparisons. For those HLA that were associated with recurrence, we further determined the effect of matching recipient and donor HLA with recurrence.

**Results**

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).

**Conclusions**

HLA profiles may be used for risk stratification of recurrence of FSGS in pediatric kidney transplant recipients and deserves further study

I**ntroduction**

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 1 2. 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 function3, and early allograft loss4. Post-transplant FSGS recurrence accounts for the majority of allograft failures in children transplanted for primary FSGS 5. The return to dialysis, sensitization for future transplants, and increased risk of recurrence for subsequent allografts becomes particularly problematic for pediatric recipients 6. 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 7-9. Risk factors for FSGS recurrence have included living donation 10-12, younger age 11,13, initial steroid sensitivity 11, white race 12, and histologic characteristics (mesangial proliferation and minimal change disease) on initial native kidney biopsy and late SRNS 14. 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 transplantation15-24. 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 (FGS) 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 FGS 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 (**Figure 1**).

*Primary and Secondary Outcomes*

Our primary outcome was recurrence of their primary disease (FSGS) as reported by the individual transplant centers. 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 using two tailed p-values. Of note, a single donor could contribute two kidneys and therefore 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 using likelihood ratio tests and two tailed p-values. Of note, generally only serological typing is reported to UNOS. Where molecular data were available, they were converted to serologic types for consistency25. For all recipient HLA loci except HLA-C, complete serologic 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 (i.e. being a hetero- or homozygote for each HLA) of these HLA in the recipient 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. Our cohort consisted of 1,196 patients. In the cohort as a whole, the median age at listing was 15 (Interquartile Range [IQR] 11-17), 43% were female, 58% were white, 36% were black, 27% were Latino, and the median BMI was 20 (IQR 17-24). Overall, 28% of patients in our cohort experienced recurrence. Patients with post-transplant FSGS recurrence were younger (median [Med] age 14 [IQR] [10-17] vs. 16 [12-18]), and had lower albumin (Med [IQR] 3.3 [2.4-3.8] vs. 3.7 [3.2-4.2]) and body mass index (Med [IQR] 19.1 [17.0-23.0] vs. 20.5 [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 (**Figure 2**, Logrank p<0.001).

*Recurrence of FSGS after Transplant is predicted by Recipient HLA*

We examined the association of HLA antigens with recurrence at any time post transplant. In **Figure 3a**, 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%. Of note, we retained HLA-B13, DR7, DR52, and DR53 with a false discovery rate of 5%. We also investigated alleles associated with early recurrence (reported within the first year post-transplant) with a false discovery rate of 5% and obtained positive associations with B13, DR7 , DR53, DQ2, and DQ8, and negative associations with DR52 and DQ6. All alleles except DQ8 were noted in our initial analysis. We next assessed a dose effect of certain antigens by determining the odds of recurrence given recipient hetero- or homozygosity (**Figure 3B**). In general, antigens showed a dose response pattern, with homozygosity causing the point estimate to be more extreme in the same direction as the heterozygote, though this trend was not observed for DQ7. Note that B13, B58, DR52, and DR53 are excluded from this analysis either due to lack of data on heterozygosity or insufficient number of heterozygotes for analysis. Since homozygotes are less common than heterozygotes, there is less power to detect differences in association between those two dosages.

*Defining a recipient HLA risk haplotype for FSGS* recurrence

Given that HLA-DR7, DR53, and DQ2 represents a common HLA haplotype26 and because we noted that these antigens were positively correlated with one another (**Figure 4**) 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). It also increases risk of early recurrence within the 1st year (OR 2.27 95% CI 1.65-3.13). Expressed as raw percentages, 27% of those with the risk haplotype recurred within the first year whereas among patients with the C3 allele, only 6% recurred in the same time period.

*Recipient HLA Antigens are associated with time to FSGS recurrence*

We assessed whether our identified recipient 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 5**. 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.

*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 (data not shown); 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 alone). This effect was confirmed when performing multiple logistic regression using an interaction term between donor and recipient antigens (OR 0.42 95**%** CI 0.37-0.53, p=0.009). Under 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 (**Table 3**). Our initial model included all terms previously seen to be significant on univariable analysis including recipient HLA (the risk haplotype [HLA-DR7-DR53-DQ2], HLA-B13, DR52, C3, B58, DQ6*,* and DQ7), recipient/donor sharing of HLA-DQ7, as well as 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, 95%CI 0.64-0.72). However, our final model was as predictive (c-statistics 0.68, 95%CI 0.64-0.71) but had an improve AIC (1098 vs. 1102) and BIC (1142 vs. 1166). The final model included the recipient risk haplotype, B58, C3, DQ6, concordance at DQ7, and age at listing as explanatory variables.

**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 genome-wide association study (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 gene discovery studies that revealed a large number of pathogenic gene variants that cause monogenic FSGS; however, these only account for approximately 30% of SRNS/FSGS cases 27,28. The majority of genes identified encode for proteins essential to the integrity29 and function of the glomerular podocyte 30. 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 31-37.Experimental and clinical data show improvement of proteinuria after treatment with plasmapheresis, which supports the hypothesis that a circulating factor contributes to podocyte injury38. 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) 39–43.

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 haplotype—HLA DR7, DR53, and DQ2—have been previously identified in multiple studies of primary NS 15–18,20-24. Additionally, all 3 of these HLA and the risk haplotype were associated with early recurrence, which is likely of more clinical concern than later recurrence. 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 44 . 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 20,21,24 in a diverse cohort. This is important, as previous examination of SNP imputation of HLA has found errors, especially in non-white populations45. Though there have been some small historical studies examining the relationship of serologic HLA type with primary NS and FSGS 46,47, 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 was mediated only by the recipient HLA, the protective effect of HLA DQ7—associated with a decreased risk of recurrence—was determined by concordance with the donor. Though the mechanism by which concordance causes protection is unclear, it is possible that HLA DQ7 molecules are less likely to present peptides which license immunologically mediated destruction leading to changes consistent with FSGS. Additionally, it is unclear if our inability to find this concordance effect more broadly is due to a true biological difference or mediation at the allelic and not the antigen level. Given that there are conflicting studies on the effect of donor factors in the risk of recurrence 10–13, 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.

More mechanistically intuitive is the fact that multiple class II HLA are associated with an increased risk of recurrence. HLA class II expression in the kidney is constitutively low, but is upregulated in response to inflammation and injury. Therefore, interaction between HLA class II and adaptive immunity generally involves the presentation of peptides in a proinflammatory environment. Indeed, studies to determine the expression of class II HLA in the kidneys of patients with FSGS may yield insights into the pathogenesis of the disease and the potential for recurrence.

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 and not compatible with monogenic FSGS which has a much lower recurrence rate 14,48. Also, all included patients are pediatric and do not have diabetes, limiting the chance of patients with secondary FSGS being included in our cohort. Our dataset does not contain diagnosis codes for other forms of NS such as minimal change disease, therefore we may be excluding some patients inappropriately. The dataset also does not contain information 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* level23. This limitation may be a reason that we did not detect associations between all previously identified HLA and recurrent FSGS. However, our identification of a common risk haplotype DR7-DR53-DQ2 adds credibility to the associations we did find. Finally, it is possible that the associations we see here implicate not HLA in the pathogenesis of FSGS but rather other variants in linkage disequilibrium with those HLA.

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 to improve donor selection, and perioperative management for pediatric patients with FSGS.

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**Disclosures**

The authors have no relevant financial disclosures.

**Data Availability Statement**

Primary data are available upon request from the corresponding author.

**Figure Legends**

**Figure 1 Legend:** Cohort definition flow diagram.

**Figure 2 Legend:** Kaplan Meier curve of death censored graft survival. Comparison by Logrank test.

**Figure 3 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 from most to least significant in from top to bottom. 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. HLA B13, B58, DR52, and DR53, not shown due to lack of information on heterozygosity or too few patients for modelling.

**Figure 4 Legend:** Association between all Recipient HLA antigens significantly associated with disease recurrence. HLA-DR7, DR53, and DQ2 are all positively correlated with one another. Pearson’s correlation coefficient shown.

**Figure 5 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.

**Table 1:** Recipient Characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No Recurrence** | **Recurrence** | **p-value** |
|  | **N=862** | **N=334** |  |
| **Gender**(Female)-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-racial | 11 ( 1%) | 6 ( 2%) |  |
| Native American | 5 ( 1%) | 1 ( 0%) |  |
| Pacific Islander | 3 ( 0%) | 4 ( 1%) |  |
| White | 493 (57%) | 203 (61%) |  |
| **Ethnicity**(Latino)-n(%) | 251 (29%) | 79 (24%) | 0.058 |
| **Time on 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**-Med(IQR) | 20.5 (17.5-24.8)^ | 19.3 (17.0-23.0)^ | **0.002** |

**Legend:** Bolded p-values are significant at p<0.05 level; \*0-5% Missing; ^5-10% Missing; &10-20% Missing; †>20% Missing

**Table 2:** Donor Characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No Recurrence** | **Recurrence** | **p-value** |
|  | **N=856** | **N=328** |  |
| **Donor Type**(Living)-n(%) | 217 (25%) | 96 (29%) | 0.17 |
| **Related Donor**-n(%) | 170 (20%) | 74 (23%) | 0.30 |
| **Donor Gender**(Female)n(%) | 338 (39%) | 136 (41%) | 0.53 |
| **Donor Age**-MED(IQR) | 25.0 (19.0-34.0) | 26.5 (19.0-38.0) | 0.12 |
| **Donor Race**-n(%) |  |  | 0.18 |
| Asian | 13 ( 2%) | 10 ( 3%) |  |
| Black | 135 (16%) | 46 (14%) |  |
| Multi-racial | 6 ( 1%) | 0 ( 0%) |  |
| Native American | 9 ( 1%) | 1 ( 0%) |  |
| Pacific Islander | 1 ( 0%) | 0 ( 0%) |  |
| White | 692 (81%) | 271 (83%) |  |
| **Body Mass Index**-Med(IQR) | 25.1 (22.2-28.8) | 24.7 (21.5-28.5) | 0.12 |
| **Inotrope Support**-n(%) | 334 (54%)† | 128 (56%)† | 0.51 |
| **Cause of Death**-n(%) |  |  | 0.044 |
| Anoxia | 135 (21%)† | 55 (24%)† |  |
| CVA | 79 (12%)† | 37 (16%)† |  |
| Head Trauma | 416 (65%)† | 133 (57%)† |  |
| CNS Tumor | 3 ( 0%)† | 0 ( 0%)† |  |
| Other | 6 ( 1%)† | 7 ( 3%)† |  |
| **Donor Diabetes**-n(%) | 5 ( 1%) | 3 ( 1%) | 0.48 |
| **Cigarette Smoking**-n(%) | 64 (10%)† | 23 (10%)† | 0.97 |
| **Cocaine Use**-n(%) | 73 (12%)† | 27 (12%)† | 0.92 |
| **Cold Ischemia Time**(Hours)-Med(IQR) | 10 (5-16)^ | 9(4-16)^ | 0.70 |

**Legend:** Bolded p-values are significant\*0-5% Missing; ^5-10% Missing; &10-20% Missing; †>20% Missing

**Table 3:** Multivariable Models for the Prediction of FSGS Recurrence

|  |  |  |
| --- | --- | --- |
|  | Initial Model | Final Model |
|  | OR (95% CI) | OR (95% CI) |
| Race (Black=1) | 0.933 | 0.873 |
| 0.661,1.318 | 0.623,1.222 |
| Ethnicity(Latino=1) | **0.648\*** | **0.654\*** |
| **0.444,0.944** | **0.451,0.948** |
| Recipient Risk Haplotype | **1.569\*** | **1.718\*\*** |
| **1.108,2.224** | **1.231,2.397** |
| Recipient DR52 | 0.802 |  |
| 0.585,1.100 |  |
| Recipient B13 | 1.472 |  |
| 0.713,3.040 |  |
| Recipient C3 | **0.270\*\*** | **0.270\*\*** |
| **0.112,0.652** | **0.112,0.650** |
| Recipient B58 | 0.551 | **0.514\*** |
| 0.283,1.072 | **0.265,0.996** |
| Recipient DQ7 | 0.93 |  |
| 0.636,1.359 |  |
| DQ7 Match | **0.361\*\*** | **0.334\*\*\*** |
| **0.195,0.670** | **0.193,0.577** |
| Age at listing | **0.932\*\*\*** | **0.931\*\*\*** |
| **0.901,0.965** | **0.900,0.964** |
| Related Donor | 1.258 |  |
| 0.856,1.828 |  |
| Constant | 1.482 | 1.371 |
| 0.840,2.615 | 0.819,2.294 |

**Legend:** Bolded p-values are significant; \* p<0.05, \*\* p<0.01, \*\*\* p<0.001

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