

# Graft Loss Due to Recurrent Lupus Nephritis in Living-Related Kidney Donation

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## Summary

**Background and objectives** Major predisposing risks for the development of SLE in the nontransplant setting have been reported to include female gender, ethnicity, and genetic factors among others. In the current study, we aimed to determine whether increasing haplotype match in living donor renal transplantation would have a negative impact on the long-term rates of graft loss due to lupus nephritis recurrence.

**Design, setting, participants, and measurements** Data were provided by the Organ Procurement and Transplantation Network—United Network for Organ Sharing. Living-related primary kidney transplants performed between January 1, 1988, and December 31, 2007 with the native renal diagnosis of lupus nephritis for all patients alive and with functioning graft at discharge were included. The cumulative probability rates of allograft loss due to recurrence of lupus nephritis (RLN) stratified by haplotype match and immunosuppression were obtained.

**Results** The cumulative probability rates of graft loss due to RLN in primary kidney transplant recipients receiving cyclosporine-based immunosuppression were 4.8% ( $n = 187$ ), 2.9% ( $n = 602$ ), and 0.7% ( $n = 192$ ) for recipients with 0-, 1-, and 2-haplotype matches, respectively. Similarly, recipients receiving “all maintenance” immunosuppressive therapy with 0-, 1-, and 2-haplotype matches had graft loss rates of 4.3% ( $n = 433$ ), 2.3% ( $n = 1049$ ), and 0.5% ( $n = 303$ ), respectively. Chi-squared analyses revealed no significant gender or ethnic background differences among haplotype groups. Compared with 0-haplotype, 1- and 2-haplotype matched recipients were generally younger.

**Conclusions** Living-related kidney donation with increasing haplotype match is unexpectedly associated with lower rates of allograft loss due to RLN. Potential contributory factors to this positive effect are not known.

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## Introduction

Renal manifestations ranging from abnormal urinalysis to varying degrees of lupus nephritis (LN) have been reported in up to 30% to 50% among patients with SLE (1,2). The relapse rates of LN in native kidneys have been reported to be 35% to 60% depending on population studied, criteria used, and maintenance immunosuppressive therapy. End-stage kidney disease secondary to LN in native kidneys has been estimated to range from 8% to 15%. Major predisposing risks for the development of SLE have been reported to include female gender, ethnicity, and genetic factors among others (3). Despite the high rates of renal involvement and relapse in native kidneys, renal transplantation involving patients with primary kidney failure due to LN has conferred excellent outcomes in terms of allograft loss due to disease recurrence at long-term follow-up. Although biopsy-proven recurrent LN (RLN) has been reported in up to 30% to 54% of renal transplant recipients, clinical recurrence rates have been estimated to be much lower at approximately 5%. Most importantly, actual

graft loss due to RLN is uncommon (3–5). The excellent long-term outcomes observed with renal transplantation in patients with the primary native kidney diagnosis of LN have been predominantly attributed to the use of chronic immunosuppressive therapy.

Risks for RLN in the renal allograft have been reported to include African-American ethnicity, female recipients, younger age, hypocomplementemia after transplantation, presence of lupus anticoagulant, and possibly living donors (4,6–9). In a retrospective analysis of the United Network for Organ Sharing (UNOS) database, Contreras *et al.* have demonstrated that the use of biologic agents for induction compared with other agents—cyclosporine compared with tacrolimus and azathioprine compared with mycophenolate maintenance immunosuppression—had no significant effect on the odds of RLN (9). Given the genetic predisposition to the development of SLE and existing evidence for a possible increased incidence of histologic, but not necessarily clinical, RLN among recipients with living donors (4), concerns regarding the potential increased risks for allograft loss due to

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RLN among living-related kidney donation are valid. In the current study, we examine the long-term rates of actual kidney allograft loss due to RLN among living kidney transplants stratified by haplotype match.

## Materials and Methods

All data were provided by the Organ Procurement and Transplantation Network (OPTN)–UNOS database. Primary living kidney transplants performed between January 1, 1988, and December 31, 2007 (as of October 29, 2010) with the native renal diagnosis of LN for all patients alive and with functioning graft at discharge were included. Baseline demographics were based on data provided at the time of transplantation. The cumulative probability rates of allograft loss due to RLN stratified by maintenance immunosuppressive therapy as reported at the time of discharge and haplotype match were obtained. Allograft loss due to RLN was based on institutional report without the requirement for biopsy-proven RLN. Patients were censored for deaths and loss to follow-up. Differences among survival curves were based on log-rank test. Differences among haplotype groups with respect to ethnicity were based on chi-squared statistics. Differences in age and gender were based on *t* test. A *P* value less than 0.05 was considered statistically significant. As cyclosporine is the most commonly used calcineurin inhibitor among kidney transplant recipients recorded in the UNOS/OPTN database, we further stratified allograft loss due to presumed RLN by immunosuppressive therapy as cyclosporine-based *versus* “all maintenance” (cyclosporine-based *and* all other) immunosuppressive therapy to minimize heterogeneity in terms of potential interaction with specific immunosuppressive regimen and outcome. Recipients of cyclosporine-based maintenance immunosuppressive therapy and recipients of all maintenance immunosuppressive therapy were reviewed separately. All recipients of multiple organ transplants were excluded.

## Results

### Demographics

The cyclosporine-based immunosuppressive therapy group consisted of 981 patients with a mean age of  $34.2 \pm 0.6$  years, 80.6% of whom were women and 53.6% were of the white race. The all maintenance immunosuppressive therapy group consisted of 1785 patients with a mean age of  $35.0 \pm 0.4$  years, 81.7% of whom were women and 48.0% were of the white race (Table 1). Demographic distributions for ethnicity and gender stratified by haplotype match were similar in all groups (Tables 2 and 3). Recipients of 1- and 2-haplotype match kidneys were generally of younger age compared with those of 0-haplotype match (Table 3).

### Cumulative Probability Rates of Allograft Loss Due to RLN

At 10-year follow-up, the cumulative probability rates of allograft loss due to RLN among recipients receiving cyclosporine-based immunosuppressive maintenance therapy were 4.77%, 2.93%, and 0.66% for 0-, 1-, and 2-haplotype match, respectively, with a log-rank *P* value of 0.028 (Figure 1). At 10-year follow-up, the cumulative probability rates of allograft loss due to RLN among recipients

**Table 1. Patients' demographics**

	Cyclosporine-based		All Maintenance	
	<i>N</i>	%	<i>N</i>	%
Ethnic background				
white	526	53.6	857	48
black	255	26	484	27.0
hispanic	146	14.9	324	18.2
asian	22	2.2	78	4.4
others	32	3.3	42	2.4
total	981	100	1785	100
Gender				
female	791	80.6	1459	81.7
male	190	19.4	326	18.3
total	981	100	1785	100
Age (years) <sup>a</sup>	$34.2 \pm 0.6$		$35.0 \pm 0.4$	

The number of patients for each characteristic category may not match within each immunosuppressive therapy groups because of incomplete data entry. *N*, total number of patients.  
<sup>a</sup> Values are mean  $\pm$  SEM.

receiving *all* maintenance immunosuppressive therapy were 4.25%, 2.33%, and 0.45% for 0-, 1-, and 2-haplotype match, respectively, with log-rank *P* value of 0.035 (Figure 2). All three haplotype groups matched in terms of ethnicity, age, and gender distributions.

## Discussion

Concerns for the potential increased risks of kidney allograft loss due to RLN among recipients of living-related kidney donors are reasonable and valid given known genetic predispositions for the development of SLE. Nonetheless, our current study suggests that the rate of allograft loss due to RLN is significantly better among recipients receiving a living-related kidney with 2-haplotype match compared with 1- or 0-haplotype match kidneys. Although recipients of 1- and 2-haplotype match kidneys were generally younger compared with those of 0-haplotype match, previous analyses of the same database by Contreras *et al.* revealed that younger age is associated with more severe RLN and would not explain the current findings (9). The etiologies responsible for this observed positive outcome are not known.

Although it is plausible that living-related kidney transplantation with increasing haplotype match may confer a lower rate of allograft loss due to RLN because of a lower rate of concomitant kidney insults from rejections, a higher number of haplotype match has not been shown to confer a similar beneficial effect on the rates of graft loss due to disease recurrence in other glomerular diseases (10). Furthermore, in a retrospective analysis of the UNOS database, Contreras *et al.* have previously demonstrated that recipients with RLN alone and recipients with RLN with rejection had a similarly poor allograft survival (9).

The authors speculate that patients with SLE may develop a form of protective autoimmunity after the initial development of LN in the native kidneys. Protective autoimmunity, first described in the neuroimmunology literature by Schwartz *et al.*, is a physiologic phenomenon whereby an initial injurious event leads to the production

**Table 2. Ethnic background distribution by haplotype**

Ethnicity	CSA-Based <sup>a</sup>			All Maintenance <sup>a</sup>		
	0-Haplotype	1-Haplotype	2-Haplotype	0-Haplotype	1-Haplotype	2-Haplotype
White	98 (52.4)	320 (53.2)	108 (56.3)	204 (47.1)	495 (47.2)	158 (52.1)
Black	50 (26.7)	157 (26.1)	48 (25.0)	116 (26.8)	297 (28.3)	71 (23.4)
Hispanic	30 (16.0)	90 (14.9)	26 (13.5)	86 (19.9)	183 (17.4)	55 (18.2)
Asian	0 (0)	2 (0.3)	0 (0)	19 (4.4)	47 (4.5)	12 (4.0)
American Indian/ Alaska native	0 (0)	0 (0)	0 (0)	0 (0)	12 (1.1)	0 (0)
Other/not reported	9 (4.8)	33 (5.5)	10 (5.2)	8 (1.8)	15 (1.4)	7 (2.3)
Total	187	602	192	433	1049	303

Chi-squared testing for major ethnic backgrounds including white, black, and Hispanics did not reveal any statistically significant difference among the three haplotype groups for either cyclosporine-based or all maintenance-based immunosuppressive therapy;  $P = 0.9$  and  $P = 0.4$ , respectively.

<sup>a</sup> Values are total number of patients with percentage in parentheses.

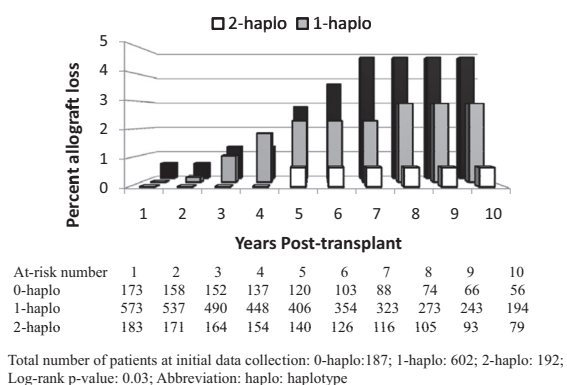
**Table 3. Age and gender distributions by haplotype**

	CSA-Based			All Maintenance		
	0-Haplotype	1-Haplotype	2-Haplotype	0-Haplotype	1-Haplotype	2-Haplotype
Age (years) <sup>a</sup>	36.1 ± 0.7	33.2 ± 0.5	35.2 ± 0.7	37.4 ± 0.5	33.8 ± 0.4	35.9 ± 0.5
$P$	0- versus 1-haplo: 0.0008; 0- versus 2-haplo: 0.4; 1- versus 2-haplo: 0.02			0- versus 1-haplo: <0.0001; 0- versus 2-haplo: <0.0001; 1- versus 2-haplo: 0.001		
Gender: female <sup>b</sup>	151 (80.7)	488 (81.0)	152 (79.0)	343 (79.2)	866 (82.6)	250 (82.5)
$P$	0- versus 1-haplo: 0.9; 0- versus 2-haplo: 0.7; 1- versus 2-haplo: 0.6			0- versus 1-haplo: 0.1; 0- versus 2-haplo: 0.3; 1- versus 2-haplo: 0.9		

Haplo, haplotype.

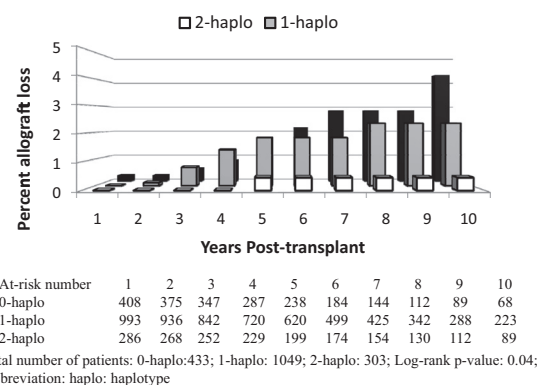
<sup>a</sup> Values are means ± SEM.

<sup>b</sup> Values are total number of patients with percentage in parentheses.



**Figure 1. | Cumulative probability rates of allograft loss due to lupus nephritis recurrence among living renal transplants stratified by haplotype: cyclosporine-based immunosuppression.**

of autoreactive protective T cells that can recognize self-antigens and promote tissue repair after a secondary tissue injury (11). Although, to our knowledge, protective autoimmunity has not been studied in patients with SLE, it is of interest to note that relapses of autoimmune diseases such as LN tend to occur early after the initial diagnosis. It is



**Figure 2. | Cumulative probability rates of allograft loss due to lupus nephritis recurrence among living renal transplants stratified by haplotype: all maintenance immunosuppression.**

conceivable that the eventual development of protective autoimmunity in patients with SLE may result in the reduction in frequency of late-disease relapse. If protective autoimmunity does indeed occur with SLE, it may explain the lower rate of allograft loss due to RLN in recipients of living-related kidneys.

Despite the observed strong and significant reduction in the rates of long-term graft failure associated with increasing haplotype match living kidney donor transplantation in patients with the primary native kidney diagnosis of LN, we acknowledge several limitations to the study including accuracy of institutional reports, underreporting of graft loss due to disease recurrence, recipient factors such as acute rejection episodes, type of immunosuppression, comorbidities, infections, malignancies, smoking, or other poor lifestyle habits, and unknown steroid and immunosuppressive medication dosages. Lastly, the UNOS database system does not have data on biopsy or clinical findings because these characteristics were not required to classify recurrences.

In conclusion, the rate of allograft loss due to RLN is lowest among recipients of living-related kidneys with increasing haplotype match. The underlying “protective” factors against allograft loss due to RLN among recipients of living-related kidneys remain to be elucidated.

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#### Disclosures

None.

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