Genomic Mismatch at LIMS1 Locus and Kidney Allograft Rejection


BACKGROUND
In the context of kidney transplantation, genomic incompatibilities between donor and recipient may lead to allosensitization against new antigens. We hypothesized that recessive inheritance of gene-disrupting variants may represent a risk factor for allograft rejection.

METHODS
We performed a two-stage genetic association study of kidney allograft rejection. In the first stage, we performed a recessive association screen of 50 common gene-intersecting deletion polymorphisms in a cohort of kidney transplant recipients. In the second stage, we replicated our findings in three independent cohorts of donor–recipient pairs. We defined genomic collision as a specific donor–recipient genotype combination in which a recipient who was homozygous for a gene-intersecting deletion received a transplant from a nonhomozygous donor. Identification of alloantibodies was performed with the use of protein arrays, enzyme-linked immunosorbent assays, and Western blot analyses.

RESULTS
In the discovery cohort, which included 705 recipients, we found a significant association with allograft rejection at the LIMS1 locus represented by rs893403 (hazard ratio with the risk genotype vs. nonrisk genotypes, 1.84; 95% confidence interval [CI], 1.35 to 2.50; P = 9.8×10⁻⁵). This effect was replicated under the genomic-collision model in three independent cohorts involving a total of 2004 donor–recipient pairs (hazard ratio, 1.55; 95% CI, 1.25 to 1.93; P = 6.5×10⁻⁵). In the combined analysis (discovery cohort plus replication cohorts), the risk genotype was associated with a higher risk of rejection than the nonrisk genotype (hazard ratio, 1.63; 95% CI, 1.37 to 1.95; P = 4.7×10⁻⁸). We identified a specific antibody response against LIMS1, a kidney-expressed protein encoded within the collision locus. The response involved predominantly IgG2 and IgG3 antibody subclasses.

CONCLUSIONS
We found that the LIMS1 locus appeared to encode a minor histocompatibility antigen. Genomic collision at this locus was associated with rejection of the kidney allograft and with production of anti-LIMS1 IgG2 and IgG3. (Funded by the Columbia University Transplant Center and others.)
Approximately 20% of the kidney waiting list in the United States consists of candidates whose allografts have failed. Acute rejection is one of the strongest predictors of decreased allograft survival. Although human genetic variation and donor–recipient genetic interactions are likely to be involved in the determination of allograft outcomes, there have been few well-designed and adequately powered genetic investigations in this area.

Even though the dramatic improvements in short-term outcomes after transplantation have not resulted in similar improvements in long-term graft survival, new genetic strategies for organ matching may offer practical means by which rejection can be avoided and graft survival can be prolonged. HLA matching has been studied extensively, with an emphasis on donor-specific HLA alloantibodies. However, the incidence of donor-specific HLA alloantibodies among all allograft recipients is relatively low (15 to 25%). Increasing evidence suggests an important role for minor histocompatibility antigens that result in immune activation without HLA-directed response. The clinical significance of minor histocompatibility antigens is highlighted by the observation that recipients of allografts from HLA-identical siblings require immunosuppression despite perfect HLA matching, and there are survival differences when analyses are stratified according to panel-reactive antibody titers. It is estimated that approximately 56% of allograft failures can be attributed to immunologic reactions, with 38% of the reactions being against non-HLA factors and only 18% being due to HLA mismatch. In the past decade, several minor histocompatibility antigens have been successfully identified. Angiotensin II type 1 (AT1) receptor is perhaps the best-studied example, with preexisting and acquired anti–AT1 receptor antibodies predicting allograft rejection and failure. Nevertheless, the overall incidence of known alloantibodies to minor histocompatibility antigens is low, which suggests that there are contributions from additional antigens.

We hypothesized that the recipient’s inheritance of variants that disrupt kidney genes predisposes the recipient to allosensitization and rejection. In this study, we tested common copy-number polymorphisms that intersect genes, since such variants have a profound effect on gene function and expression. Using a genetic association screen of high-priority deletions, we sought to identify specific loci associated with kidney allograft rejection.

Methods

Study Design and Clinical Outcome

The study design had two stages. The first stage (the discovery phase) involved a screen of 50 high-priority copy-number polymorphisms (see below) in kidney allograft recipients who had undergone transplantation at the Columbia University Irving Medical Center in New York. Signals that reached a P value of less than 0.05 were advanced to the second stage (the replication phase). The replication phase involved genotyping of the top signals from the discovery phase in additional cohorts involving donor–recipient pairs. The primary outcome in the genetic association study was the first rejection in a time-to-event analysis, defined as a rejection event (antibody-mediated rejection or T-cell–mediated rejection) that occurred between the date of transplantation and the date of allograft biopsy showing such an event.

Discovery Phase

We used a publicly available catalogue of known copy-number variants generated with the use of 2.1 M NimbleGen comparative genome hybridization arrays. From this data set, a total of 3266 copy-number variants were mapped to the human reference genome hg18 (accessed July 2010). To optimize the power of this study, we selected only copy-number polymorphisms that had a global minor allele frequency of more than 10%, corresponding to the expected homozygosity rates of more than 1% (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Next, we intersected this set with a transcribed segment of the genome to identify potential gene-disrupting variants. A total of 180 gene-intersecting copy-number polymorphisms met our criteria, of which 87 (48%) were deletions. On the basis of the HapMap3 data, we found a single-nucleotide polymorphism (SNP) that was an informative tag (r2>0.8) for 50 (57%) of the identified deletions. These were prioritized for targeted genotyping in the discovery cohort, which involved 705 kidney recipients who had undergone transplantation at Columbia University and had been followed for a mean of...
For the 50 genotyped SNPs, we performed strict quality-control analysis of genotypes that included per-SNP and per-recipient genotyping rates of more than 95%, elimination of monomorphic SNPs, and elimination of markers that significantly deviated from the Hardy–Weinberg equilibrium within each ethnic group. In total, 44 SNPs passed all the quality-control filters (Fig. 1, and Table S3 in the Supplementary Appendix).

**Replication Phase**

The replication cohorts (Table S4 in the Supplementary Appendix) included the Belfast cohort (387 donor–recipient pairs; mean follow-up, 9.2 years; overall rejection rate, 24%), the TransplantLines Genetics cohort (833 donor–recipient pairs; mean follow-up, 6.6 years; overall rejection rate, 36%), and the Torino cohort (784 donor–recipient pairs; mean follow-up, 9.6 years; overall rejection rate, 22%), providing a total of 2004 donor–recipient pairs for analysis. The genotype quality-control and analytical procedures that we used for replication were similar to those used in the discovery phase (see the Supplementary Methods section in the Supplementary Appendix).

**Molecular Analyses**

Detailed methods regarding the deletion breakpoint mapping, functional genomic annotations, sequence motif analysis, tissue immunohisto-
Results

Discovery Phase
To test for the effect of deletion homozygosity on the risk of rejection, we used time-to-event survival analysis under a recessive model for the deletion-tagging allele. In the Kaplan–Meier analysis, we observed that a single SNP (rs893403) surpassed a Bonferroni-corrected significance threshold and reached a false discovery rate of 0.3%. Kidney transplant recipients who were homozygous for the deletion-tagging allele had an approximately 84% higher risk of rejection than those who did not have this genotype (hazard ratio, 1.84; 95% confidence interval [CI], 1.35 to 2.50; P=9.8×10⁻⁵) (Fig. 2A). This effect was robust to adjustments for ethnic group (adjusted hazard ratio, 1.80; 95% CI, 1.32 to 2.45; P=2.0×10⁻⁴) as well as for age, sex, donation type, HLA-mismatch status, and sensitization risk factors, including history of transplantation, transfusion, and pregnancy (adjusted hazard ratio, 1.83; 95% CI, 1.31 to 2.53; P=2.9×10⁻⁴). The top SNP, rs893403, represented a near-perfect tag for a 1.5-kb deletion on chromosome 2q12.3 (CNVR915.1, r²=0.98).

Replication Phase
We genotyped rs893403 in kidney transplant recipients and their matched donors from three international kidney transplant cohorts (the Belfast, TransplantLines, and Torino cohorts). After standard genotype quality control was assessed, there were 2004 donor–recipient pairs available across the three replication cohorts. For each replication cohort, we first applied the same approach as in the discovery phase, using the recipient’s homozygosity for the deletion-tagging allele as a predictor in the model of rejection. Despite the diversity of our replication cohorts, we found a direction-consistent effect of the risk genotype in all three cohorts (Table S5 in the Supplementary Appendix), and a combined meta-analysis confirmed that recipients with the risk genotype had a higher risk of acute rejection than those with a nonrisk genotype independently of age, sex, donation type, HLA-mismatch status, and transplantation center (adjusted hazard ratio, 1.41; 95% CI, 1.14 to 1.74; P=1.6×10⁻³). In the combined stratified analysis of the discovery and replication cohorts, a high-risk genotype conveyed a risk of rejection that was 50% higher than that observed with a nonrisk genotype (adjusted hazard ratio, 1.50; 95% CI, 1.26 to 1.79; P=5.4×10⁻⁴). The significance of this association surpassed our prespecified Bonferroni-adjusted threshold (alpha level of 1.1×10⁻³).

Subsequently, we used the genetic information from the donor–recipient pairs to test the genomic-collision hypothesis. The risk of genomic collision was defined according to recipient homozygosity in the absence of donor homozygosity. In findings consistent with our hypothe-
sis, the effect estimates became larger after the analysis accounted for donor genotypes within each cohort as directly compared with recipient-only analyses (Table 1). The effect estimates were direction-consistent and similar in magnitude in each of the three replication cohorts, with adjusted hazard ratios of 1.77 (95% CI, 1.06 to 2.93; $P=2.8\times10^{-2}$) in the Belfast cohort, 1.58
LIMS1 mismatch and kidney allograft rejection

In the TransplantLines cohort, and 1.53 (95% CI, 1.05 to 2.23; P = 6.6×10−3) in the Torino cohort. In the combined stratified analysis of all the replication data sets, the donor–recipient pairs with the collision genotype had a risk of allograft rejection that was 58% higher than the risk among pairs without the collision genotype, and this effect was significant (adjusted hazard ratio, 1.58; 95% CI, 1.27 to 1.97; P = 5.7×10−3) (Fig. 2B).

Next, we performed a pooled analysis of all four cohorts, which involved 2709 transplants (in 705 unmatched recipients from the discovery phase and in 2004 donor–recipient pairs from the replication phase). We note that the inclusion in this analysis of the Columbia cohort, which lacked donor genotype data, resulted in an expected predictor misclassification frequency of 1.7% in the combined data set, biasing the result slightly toward the null. Despite this limitation, the collision genotype was associated with the rejection risk, reaching genomewide significance (hazard ratio, 1.63; 95% CI, 1.37 to 1.95; P = 4.7×10−8) (Fig. 2B).

Although our study was not adequately powered to test for the association with allograft failure, we observed a nonsignificantly higher risk of failure in the collision genotype group than in the noncollision genotype group (adjusted hazard ratio, 1.12; 95% CI, 0.90 to 1.39; P = 0.32) (Fig. S5 in the Supplementary Appendix).

**Functional Annotation of the 2q12.3 Locus**

The top SNP, rs893403, resides on chromosome 2q12.3 in the intronic portion of LIMS1. This gene encodes a protein that is involved in cell adhesion and integrin signaling found in focal adhesion plaques. The risk allele, rs893403-G, is frequent in persons of European and African ancestry but absent in persons of East Asian ancestry and tags a common 1.5-kb deletion (CNVR915.1) that is downstream of LIMS1 (r²=0.98 in the HapMap European population). CNVR915.1 was originally annotated to intersect LOC100288532, a gene in the human reference genome hg18 that was removed in subsequent releases of the human genome. Our deletion breakpoint mapping and detailed functional annotations of the region indicated that the rs893403-G risk allele was associated with lower messenger RNA (mRNA) expression of LIMS1 and GCC2, the neighboring gene, across multiple GTEx project tissues than was the alternative allele of unknown function (Table S8 in the Supplementary Appendix).

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**Table 1. Cox Proportional-Hazards Association Analysis of LIMS1 Collision Genotype with Allograft Rejection in a Time-to-Event Analysis, According to Cohort.**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Population</th>
<th>Minimally Adjusted Model*</th>
<th>Fully Adjusted Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Columbia discovery cohort</td>
<td>705 Recipients</td>
<td>1.84 (1.35–2.50)</td>
<td>9.8×10−5</td>
</tr>
<tr>
<td>Belfast replication cohort</td>
<td>387 Donor–recipient pairs</td>
<td>1.70 (1.03–2.82)</td>
<td>4.0×10−2</td>
</tr>
<tr>
<td>TransplantLines replication cohort</td>
<td>833 Donor–recipient pairs</td>
<td>1.53 (1.13–2.09)</td>
<td>6.6×10−3</td>
</tr>
<tr>
<td>Torino replication cohort</td>
<td>784 Donor–recipient pairs</td>
<td>1.49 (1.02–2.16)</td>
<td>3.9×10−2</td>
</tr>
<tr>
<td>All replication cohorts</td>
<td>2004 Donor–recipient pairs</td>
<td>1.55 (1.25–1.93)</td>
<td>6.5×10−5</td>
</tr>
<tr>
<td>All cohorts</td>
<td>2709 Transplants</td>
<td>1.63 (1.37–1.95)</td>
<td>4.7×10−8</td>
</tr>
</tbody>
</table>

* The analysis was adjusted for cohort only (if applicable).
† The analysis was adjusted for recipient’s age, sex, race, ethnic group, HLA-mismatch status, and cohort (if applicable).
allele. Furthermore, rs893403 has a direction-consistent cis-eQTL effect on the LIMS1 mRNA level in the kidney tubulointerstitium. (Details are provided in the Supplemental Results section, Table S8, and Figs. S6 through S13 in the Supplementary Appendix.)

Using immunohistochemical studies, we confirmed that LIMS1 was strongly expressed in human kidneys and other commonly transplanted organ tissues, such as heart and lung. Within the kidney, LIMS1 staining is strongest in the distal nephron, including the basolateral surface of distal tubules in the cortex and medulla, the mediullary thick ascending limb of the loop of Henle, and medullary collecting ducts. The proximal-to-distal gradient of LIMS1 expression was consistent with human kidney single nuclear RNA sequencing data and was confirmed by means of RNAscope in situ hybridization. Moreover, cell-surface LIMS1 was induced by hypoxia in HEK293 cell lines, a finding consistent with previously reported hypoxia-induced LIMS1 gene expression in cultured endothelial cells.25 In contrast, GCC2 was detected predominantly in the cytoplasmic compartment of proximal tubules (most strongly in S3) and in kidney vascular smooth muscle. (Details are provided in Table S10 and Figs. S14 through S19 in the Supplementary Appendix.)

SEROREACTIVITY AGAINST LIMS1 IN RECipients WITH A HIGH-RISK GENOTYPE

To obtain an unbiased characterization of alloantibody response in kidney recipients with a high-risk genotype, we used ProtoArray protein arrays to screen serum specimens that had been obtained from recipients. These protein arrays capture the human proteome with 9375 proteins (0.15th percentile) on the array. Despite the small sample size in this experiment, the LIMS1 protein ranked 14th among the 9375 proteins (0.15th percentile) on the array according to the mean intensity in the group of recipients with a high-risk genotype who had rejection. Among the 14 top intensity signals, LIMS1 seroreactivity was most specific to the high-risk rejection group (P = 0.002 for high-risk genotype with rejection vs. all other groups) (Fig. 3A and 3B). No other proteins were encoded within a 1-Mb window of rs893403 showed significant seroreactivity, although the GCC2 protein was not captured on protein arrays. Finally, we detected a lower-intensity signal for the LIMS2 protein, which
shares 92% sequence identity with LIMS1, thus suggesting potential cross-reactivity (P = 0.007) (Fig. S20 in the Supplementary Appendix).

To confirm the protein array findings, we obtained serum specimens from 318 transplant recipients across seven genotype- and phenotype-discordant groups. We detected highly specific IgG reactivity toward LIMS1 in the kidney recipients with a high-risk genotype who had allograft rejection but not in any other control group (Fig. 3C). Next, we investigated whether an antibody targeting LIMS1 could be injurious. Treatment of cultured human kidney cortical epithelial cells expressing the LIMS1 protein with mouse antihuman LIMS1 antibody disrupted the normal organization of F-actin filaments and showed significant cytotoxicity on lactate dehydrogenase assay as compared with a nonspecific control antibody (Figs. S22 and S23 in the Supplementary Appendix).
IgG subclass analysis showed that the anti-LIMS1 response was predominantly of IgG2 and IgG3 subtype, but weaker IgG4 reactivity was also detected (Fig. 3D through 3G, and Fig. S21 in the Supplementary Appendix). Of 31 recipients with a high-risk genotype who had rejection, 26 (84%) and 23 (74%) tested positive for anti-LIMS1 reactivity by IgG2 and IgG3, respectively. Overall, 29 recipients (94%) tested positive by either IgG2 or IgG3 subtype. IgG2 and IgG3 comprise only a small percentage of total IgG (up to 30% and 8%, respectively), and there were no detectable differences between groups in levels of IgG1, the main IgG subclass, which explains why total IgG had overall lower reactivity than these subtypes.

DISCUSSION

In this study, we examined a genomic-collision scenario in which an allograft recipient was homozygous for a deletion polymorphism and received a kidney allograft from a donor who had at least one normal allele. In the analysis of four large kidney transplant cohorts, we found that the genomic collision at chromosome 2q12.3 led to a risk of rejection that was nearly 60% higher than the risk among donor–recipient pairs with noncollision genotypes. The risk associated with the collision genotype is equivalent to a mismatch of three of six HLA alleles, which is both clinically significant and potentially modifiable by genetic testing and matching. The genomic collision at chromosome 2q12.3 would be expected to occur in approximately 12 to 15% of transplants from unrelated donors among persons of European and African ancestry but would be very rare among persons of East Asian ancestry.

In our study, the collision genotype was associated with the presence of anti-LIMS1 antibodies. We also found that the risk genotype was associated with a lower kidney mRNA level of LIMS1 and that LIMS1 protein was induced on the cell surface under hypoxic conditions. The recessive model potentially supports a loss-of-function effect, and our data point to LIMS1 as the most likely culprit gene, but the precise causal variant underlying this locus is still unclear. We note that rs893403 also regulates mRNA expression of GCC2, encoding a protein of unclear function. We found that the GCC2 protein is expressed in proximal tubule cells, but because recombinant GCC2 is not available and this protein was not captured on protein arrays, we were unable to test for seroreactivity against GCC2 in this study. Further genotype-specific analysis of expression patterns of genes within the LIMS1 locus may be useful, especially in the context of hypoxic injury and other forms of injury.

Several other lines of evidence suggest that genomic incompatibilities beyond the traditional ABO and HLA loci are predictive of allograft rejection. For example, female recipients of organs from male donors are at greater risk for poor graft outcomes, probably because of sensitization to minor histocompatibility antigens encoded on the Y chromosome.32-31 The occurrence of aggressive post-transplantation antiglomerular basement membrane disease in persons affected by the Alport syndrome owing to collagen IV mutations, including loss-of-function variants, exemplifies another proof of concept for this phenomenon.32,33

Taken together, our results provide support for genomic collision at chromosome 2q12.3 contributing to the risk of allograft rejection and point to LIMS1 as a potential minor histocompatibility antigen encoded by this locus. In addition, we found that the LIMS1 protein was expressed in other commonly transplanted tissues, such as the heart and lung, but follow-up studies will be useful in determining whether our findings are generalizable to other organs. The reverse of our hypothesis has previously been tested in the context of bone marrow transplantation: the immune system of a donor who was homozygous for a gene-disrupting deletion may recognize epitopes that are encoded by that gene in the tissues of a recipient, leading to graft-versus-host disease.22 A similar mechanism may also apply to other types of variants that were not examined in this study, such as loss-of-function variants, variants altering the expression of immunogenic proteins, or missense variants that create new immunogenic epitopes. A population-based sequencing study has shown that a large proportion of persons are natural “human gene knockouts” (i.e., have two copies of loss-of-function variants in the same gene) for a num-
ber of nonessential genes. Given our hypothesis, we speculate that such persons may be at risk for rejection if they receive an allograft expressing an intact protein.

To our knowledge, the LIMS1 locus has not been detected in previous genomewide association studies of kidney transplant rejection. We suspect that this is probably due to the limited sample size of earlier studies and to the fact that limited research has been done in testing the genomic-collision model. Previous studies have involved recipient-only analyses or a standard additive genotype coding scheme. On the basis of the observed minor allele frequency and the pooled additive effect estimate for the rs893403-G allele in our cohorts, we estimated that our study would have no more than 3.5% power to detect this locus at a Bonferroni-corrected alpha level under additive coding in our discovery cohort. We also estimated that in a recipient-only genomewide association study under an additive model, a minimum of 13,000 kidney transplant recipients would need to be enrolled for the study to have 80% power for detection of this locus at a genomewide significant alpha level of $5 \times 10^{-8}$ (assuming a minor allele frequency of 0.50 and a rejection rate of 33%). Although large-scale efforts in genomewide association studies of kidney transplantation are under way, the largest discovery study of allograft rejection that we are aware of involved only 2094 kidney transplants. It remains to be seen whether the combination of genomic profiling with proteome-wide antibody screens can be used effectively to uncover new histocompatibility antigens and potentially improve the precision of organ matching.

The views expressed in this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health (NIH), New York State, or Columbia University.

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## Appendix

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REFERENCES


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