Analysis of OPTN/UNOS registry suggests the number of HLA matches and not mismatches is a stronger independent predictor of kidney transplant survival

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HLA matching and mismatching, while inversely related, are not exact opposites. Here we determined the independent effects of HLA matching and mismatching on outcomes in deceased donor kidney transplant recipients. The United Network for Organ Sharing database (1995–2012) was utilized and analyzed for delayed graft function, one-year acute rejection, and death-censored graft survival using combined multivariable models including HLA matching and mismatching. Sensitivity analyses were performed using the subgroup of deceased donor kidney transplant patients after 2003 with more uniform HLA nomenclature and resampling analyses using bootstrapping on complete data available from 96,236 recipients. Individually, both HLA matching and mismatching showed significant associations with graft survival. Adjusting the model to take into account both matching and mismatching simultaneously, the degree of HLA mismatching lost significance while matching continued to have a significant prediction for delayed graft function, the one-year acute rejection rate, and graft survival. Sensitivity analyses and bootstrapping showed similar results for all studied outcomes. Thus, analysis of this large cohort demonstrates the apparent greater association of HLA matching over HLA mismatching on both early allograft events as well as graft survival. Future analyses should preferentially utilize HLA matching as a covariate over mismatching for accurately reflecting impact on graft outcomes.

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Increased human leukocyte antigen (HLA)-matching between donor and recipient has been repeatedly associated with improved graft survival in kidney transplantation.[1–4] This has led to the development of the Organ Procurement and Transplantation Network's (OPTN) kidney allocation policy of mandatory sharing for zero antigen-mismatched kidneys in patients with calculated panel reactive antibody >20%, and up to 2 points are assigned for a zero HLA-DR mismatch.[5] In spite of these policies, immune-related inflammation and progressive graft dysfunction remain the most important causes of long-term graft loss in single-center studies in the era of modern immunosuppression.[6] Large database studies affirm that the additive signal for the hazard of graft-loss proportional to levels of HLA mismatches is still maintained.[3,4] Others have argued that simply adding up the number of HLA-mismatched alleles while allotting organs adds little benefit given the present limitations in the donor pool and the efficacy of current immunosuppressive therapies.[7–9] Meanwhile, observational, biomarker-based and interventional research studies continue to use HLA matching or HLA mismatching as predictor variables for graft outcomes.

Many publications refer to HLA matching and HLA mismatching interchangeably. The absence of a mismatch is strongly and inversely correlated with the presence of a match. However, due to the occurrence of allelic duplication at the A, B, and DR loci, and the existence of alleles that are not identifiable by the current polymerase chain reaction probes/primers, the two terms are not synonymous. An illustrative example is shown in Figure 1. The hypothetical recipient would be 0-mismatched with each of the 3 potential donors shown here; yet donors 1, 2, and 3 would be 3-, 5- and 6-antigen matched with this same recipient, respectively. Independent of levels of HLA-mismatching, non-HLA genetic loci have been implicated in allorecognition[10] and associated with the recipient alloimmune response.[11–13] Hence, we hypothesized that HLA matching may be a surrogate for increased minor *loci* similarities that are not entirely mirrored by the number of HLA mismatches.

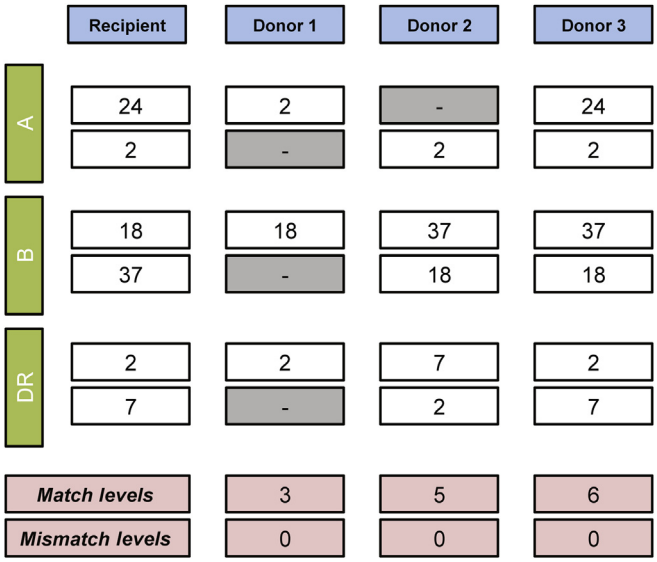

Figure 1 | Illustrative example of different levels of human leukocyte antigen (HLA)-matching within the same level of mismatch. In the United Network for Organ Sharing/Organ Procurement and Transplantation Network database, recipient 1 would have 0 mismatches (A, B, and antigen D-related [DR] loci) with each of the donors 1, 2, and 3. On the other hand, recipient 1 would be 3-, 5-, and 6-matched with donors 1, 2, and 3, respectively. Similarly, within each level of mismatch between donor and recipient, several different match levels are possible and vice versa.

Owing to the reporting of matches and mismatches in the United Network for Organ Sharing (UNOS), we tested the hypothesis that HLA matching has more significant correlation with allograft outcomes than HLA mismatching does. To examine this, we retrospectively examined the UNOS database including all deceased-donor kidney transplants from 1995 to 2012.

RESULTS

Study population (1995–2012)

A total of 96,236 deceased-donor kidney transplants were included based on complete available data (Figure 2). The mean follow-up of the entire cohort was 1482.5 days (median: 1105 [interquartile range: 382, 3163]). We defined 7 levels of HLA matches and mismatches (0–6 in both categories). Supplementary Tables S1A and S1B describe clinicodemographic characteristics within each level of HLA matching and HLA mismatching. As shown in Supplementary Figure S1, the distributions of transplant recipients of deceased donor kidney within the UNOS cohort by levels of HLA matching and HLA mismatching are not exact inverses. The matrix distribution of patients according to their levels of HLA matching and HLA mismatching in the entire cohort (Table 1) confirms that significant proportions of transplant recipients studied at each level of mismatch had discordant levels of matches in all categories (i.e., where number of matches was not equal to 6 – number of mismatches). The maximum concordance, was observed between 1-match and 5-mismatch (83.8%) and minimum concordance was observed between 0-mismatch and 6-match (33.4%) (Table 1, bold values).

HLA-match level has greater association with DGF than the HLA-mismatch level

To determine whether HLA matching or HLA mismatching demonstrated greater association with delayed graft function (DGF), we evaluated the effects of HLA matching and HLA mismatching on DGF risk (see Materials and Methods). We hypothesized that early alloimmune inflammation contributes to or prolongs DGF and would in turn be influenced by the level of HLA matching or HLA mismatching.[14,15] When individually analyzed in separate multivariate models, both matching and mismatching had significant associations with DGF, relaying the role of early alloinflammation in DGF (Figure 3a and b). However, when both match and mismatch were analyzed in a combined model, HLA-match levels had clear and significant association with DGF while HLA-mismatch levels had no impact (Figure 3c and d). In the sensitivity analyses, we generated similar logistic regression models for the subset from 2003 to 2012 with more homogenous HLA nomenclature (n = 70,759; see Materials and Methods). The mean follow-up of this 2003 cohort was 1072.8 days (median: 926 [interquartile range: 362, 1658]). The relationship between HLA-match levels and DGF, and the absence of significant association with HLA-mismatch levels, were consistent when the cohort after 2003 was separately examined (Figure 3e and f). Resampling analysis using bootstrapping technique with 10,000 iterations with resubstitution revealed similar results.

HLA-match level has greater association with 1yr-AR than the HLA mismatch level

Next, we examined the relationship of HLA matching and HLA mismatching on the outcome of clinical acute rejection within 1 year posttransplantation (1yr-AR). We used the data regarding early clinical 1yr-AR that is reported within the UNOS database. Individually both HLA matching and HLA mismatching associated significantly with 1yr-AR as an outcome (Figure 4a and b). When we input both in the same adjusted model (see Materials and Methods), we observed again that HLA-match levels were significantly predictive of 1yr-AR while HLA mismatching lost significance (Figure 4c and d). This effect of HLA matching levels on 1yr-AR and the absence of significant association with HLA-mismatching levels were consistent when the cohort after 2003 was separately examined (Figure 4e and f). Resampling analysis using bootstrapping technique with 10,000 iterations with resubstitution yielded similar results.

Sensitivity analysis. Due to the known significant impact of DGF on the risk of 1yr-AR (adjusted hazard ratio: 1.79; 95% confidence interval: 1.71–1.89 in the UNOS cohort; $P < 0.001$), and to further examine the interaction of DGF with HLA matching on the risk of 1yr-AR, we studied 1yr-AR risk in models in patients without DGF. In patients without DGF, HLA matching, and not HLA mismatching, had a significant effect on 1yr-AR risk in a combined model