Title

HLA and Risk of Diffuse Large B cell Lymphoma After Solid Organ Transplantation

Journal

Transplantation, 100(11)

ISSN

0041-1337

Authors

Hussain, Shehnaz K
Makgoeng, Solomon B
Everly, Matthew J
et al.

Publication Date

2016-11-01

DOI

10.1097/tp.0000000000001025

Peer reviewed

HHS Public Access

Author manuscript

Transplantation. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Transplantation. 2016 November ; 100(11): 2453–2460. doi:10.1097/TP.0000000000001025.

HLA and risk of diffuse large B-cell lymphoma after solid organ transplantation

Shehnaz K. Hussain[1,2], **Solomon B. Makgoeng**[2], **Matthew J. Everly**[3], **Marc T. Goodman**[1], **Otoniel Martínez-Maza**[2,4], **Lindsay M. Morton**[5], **Christina A. Clarke**[6], **Charles F. Lynch**[7], **Jon Snyder**[8], **Ajay Israni**[8], **Bertram L. Kasiske**[8], and **Eric A. Engels**[5]

[1]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

[2]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA

[3]Terasaki Foundation Laboratory, Los Angeles, CA

[4]Departments of Obstetrics and Gynecology and Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA

[5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

[6]Cancer Prevention Institute of California, Fremont, CA; Division of Epidemiology, Department of Health Research and Policy and Medicine, Stanford University School of Medicine, Stanford, CA

[7]Department of Epidemiology, University of Iowa, Iowa City, IA

[8]Scientific Registry of Transplant Recipients and Minneapolis Medical Research Foundation, Minneapolis, Minneapolis, MN

Abstract

Background—Solid organ transplant recipients have heightened risk for diffuse large B-cell lymphoma (DLBCL). The role of donor-recipient HLA mismatch and recipient HLA type on DLBCL risk are not well established.

Methods—We examined 172,231 U.S. kidney, heart, pancreas, and lung recipients transplanted between 1987 and 2010, including 902 with DLBCL. Incidence rate ratios (IRRs) were calculated using Poisson regression for DLBCL risk in relation to HLA mismatch, types, and zygosity, adjusting for sex, age, race/ethnicity, year, organ, and transplant number.

Results—Compared to recipients who had two HLA-DR mismatches, those with zero or one mismatches had reduced DLBCL risk, (zero: IRR=0.76, 95%CI=0.61–0.95; one: IRR=0.83, 95%CI=0.69–1.00). In stratified analyses, recipients matched at either HLA-A, -B, or -DR had a significantly reduced risk of late-onset (>2 years after transplantation), but not early-onset,

Correspondence: Shehnaz K. Hussain, Cancer Prevention and Control Research, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd., SCCT 1S31, Los Angeles, CA 90048; shehnaz.hussain@cshs.org.

Contribution: S.K.H. and E.A.E. conceived the study and participated in the research design and data analysis. S.B.M. participated in the data analysis. M.T.G., C.F.L., J.S., A.I., and B.L.K. participated in data acquisition and research design. M.J.E., O.M.M., L.M.M., and C.A.C. participated in the research design. All authors participated in the writing of the manuscript.

Conflict-of-interest disclosure: The authors of the manuscript have no competing financial interests.

DLBCL, and there was a trend for decreasing risk with decreasing mismatch across all three loci (P=0.0003). Several individual recipient HLA-A, -B, -C, -DR, and –DQ antigens were also associated with DLBCL risk, including DR13 (IRR=0.74, 95%CI=0.57–0.93) and B38 (IRR=1.48, 95%CI=1.10–1.93), confirming prior findings that these two antigens are associated with risk of infection-associated cancers.

Conclusions—In conclusion, variation in HLA is related to susceptibility to DLBCL, perhaps reflecting intensity of immunosuppression, control of Epstein-Barr virus infection among transplant recipients, or chronic immune stimulation.

Introduction

Non-Hodgkin lymphoma (NHL) is the most common *de novo* malignancy, apart from nonmelanoma skin cancer, in solid organ transplant recipients. Diffuse large B-cell lymphoma (DLBCL) is the most common NHL subtype in the post-transplant setting, comprising approximately 73% of specified NHL subtypes.[1] On average, DLBCL risk is 12 times higher in solid organ transplant recipients than in the general population, and risk is even higher in specific subgroups, including children and lung or pancreas recipients.[2–5] DLBCL is also the most common cause of cancer-related deaths.[6,7]

Multiple factors likely contribute to the etiology of DLBCL in transplant recipients. A large fraction of cases is attributed to Epstein–Barr virus (EBV), which in absence of host immune control, drives lymphocyte proliferation. However, the occurrence of DLBCL in long-term transplant survivors appears to be caused by factors in addition to EBV.[2,8,9]

Human leukocyte antigens (HLAs) display foreign antigens to the immune system, thereby playing a central role in the generation of adaptive immune responses. The genes for HLA class I (HLA-A, -B, and -C) and class II (HLA-DRB1, -DQB1, and -DPB1) are the most polymorphic of all genes in mammals.[10] Distinguishing between self and nonself antigens is an essential task of HLA, which is critical in transplant immunity, and differences in HLA between donor and recipient can cause transplant rejection. In a landmark study published in 1969, Patel and Terasaki showed that the presence of anti-donor HLA antibodies was a major determinant of immediate graft loss.[11] Even in the modern era of effective immunosuppressive medication regimens, HLA matching of donors to recipients remains an important component for placing donor organs for kidney transplantation, and there is accumulating evidence that HLA matching is beneficial for allograft and patient survival among recipients of lung, liver, and heart transplants.[12,13,14] Other long-term effects associated with HLA incompatibility among solid organ transplant recipients, such as risk for developing DLBCL, have been largely unexplored.

In the general population, genetic variation in HLA has been associated with susceptibility to numerous infections and immunological diseases, including cancers with infectious origins.[15–18] Several previous genetic association studies targeting HLA, as well as genome-wide association studies, identified variants in HLA genes that were significantly associated with NHL susceptibility in the general population, including polymorphisms in HLA-B, HLA-DRB1, HLA-DQB1, and carriership of the ancestral haplotype HLA 8.1 (HLA-A:01-

B:08-DR:03-TNFG-308A).[19–25] It has also been observed that people who are homozygous for all three HLA class I alleles have an increased risk of DLBCL.[19]

Serologically defined HLA antigens are characterized for the majority of recipients for organ matching and/or evaluating immune risk. Serological methods assess HLA cell surface expression and so differ from the methods used in the previously summarized studies of HLA and NHL, which delineate genetic sequences in HLA. Several prior studies have examined the associations between HLA variants and susceptibility to DLBCL among solid organ transplant recipients, but due to the small study populations, the findings were variable.[26–28]

Understanding the role of HLA may shed light on the development of lymphomas in solid organ transplant recipients. To comprehensively evaluate the association between donor-recipient HLA mismatch, individual HLA recipient antigens, and post-transplant DLCBL risk, we examined data from the Transplant Cancer Match (TCM) Study, a U.S. study of solid organ transplant recipients with systematic registry-based ascertainment of cancer outcomes.

Materials and methods

Detailed methods for the TCM Study (http://transplantmatch.cancer.gov/) have been published.[29] In summary, the TCM Study is a linkage of the U.S. Scientific Registry of Transplant Recipients (SRTR, 1987–2010) with 15 U.S. population-based state or metropolitan area cancer registries. The SRTR includes structured data on all U.S. solid organ transplants including recipient demographics, transplant characteristics, and HLA type for the organ donor and recipient. The cancer registries collect standardized information on patient demographic characteristics and detailed tumor characteristics for all state-mandated reportable cancer cases. Record linkages were conducted using a computer-based matching algorithm followed by clerical review for confirmation of potential matches, resulting in coverage of approximately 46.2% of the U.S. transplant population from 1987 to 2010. The TCM Study was approved by human subjects research review committees at the National Cancer Institute and at participating cancer registries, as required.

In this study, transplant recipients were eligible if they had follow-up time (as defined below) covered by a participating cancer registry. From a total of 230,170 transplants, liver transplants were excluded (23.0%) because nearly half had no HLA data. Additionally, we excluded 2.6% of recipients of organs other than liver who had no HLA data, and <0.1% who were HIV-infected.[30] After exclusions, our analytic cohort included 172,231 transplants. DLBCL diagnoses were assessed in the cancer registries using International Classification of Diseases for Oncology, 3rd Edition morphology codes 9678–9680 or 9684.

Transplant recipients were considered at risk of DLBCL beginning at transplantation or the start of cancer registry coverage (whichever came later). Follow-up ended at first occurrence of a DLBCL diagnosis, death, failure of a transplanted organ, subsequent transplant, loss to follow-up, or last date of cancer registry coverage. Individuals were not excluded on the basis of a history of cancer prior to transplantation, and were not censored if they were

diagnosed with a cancer (other than DLBCL) after transplantation. Recipients were considered at risk separately during successive transplant episodes. Hispanics were followed beginning in 1992 to correspond to the years for which general population cancer rates were available.

Mismatch for HLA-A, -B, and –DR was determined by the SRTR variable for mismatch according to the historic matching standard at the time of transplantation. For each locus, the mismatch variable was categorized as 0, 1, or 2 mismatches. The total number of mismatched loci across A, B, and DR loci (ranging from 0 to 6) was calculated by adding up the mismatches at each locus.

Data on individual alleles at recipient HLA class I loci (A, B, and C) and class II loci (DR and DQ) were also determined from the SRTR records. Recipient HLA antigens were categorized as present versus absent for each locus. Rare antigens (present in less than 500 transplant records) were excluded from these analyses. Since each individual has two antigens, an antigen could be present once or twice in the same individual. We also classified recipients at each locus as homozygous (all recipients who had two of the same antigens) or heterozygous (all recipients who had different antigens). When only one antigen was identified for a given locus, the recipient was considered to be homozygous for the present antigen. If a recipient was missing both antigens at a locus, the record was dropped from the analysis of that locus only. HLA-A, -B, and –DR antigen data were missing for less than 1% of the cohort. HLA-C and –DQ antigen data were missing in a more substantial fraction of the study population (36.0% and 15.2% missing, respectively). HLA-DP was not examined because it was missing in 99.8% of the study population.

HLA antigen classifications have evolved over time as tissue typing has changed from serotyping to cellular typing to DNA-based genotyping. These testing developments have allowed for the detection of differences in antigens (“split” categories) that were previously undistinguishable (“broad” categories). Our study included 21 groups of antigens that were affected by broad categories splitting over time. We used information on the frequencies of the broads/splits in each group and the year at which the splits came into existence to determine whether antigens would be analyzed as distinct split categories or harmonized by combining the broads and splits into a single category. Details are presented in supplementary materials. Briefly, 11 of these antigen groups contained broad categories that were almost completely phased out of use by 1987 (initial year for this study), thus each split category was analyzed separately and the rarely used broad categories were excluded. For four antigen groups, due to rarity of one or more of the split categories, broads and splits were harmonized into a single category. For six antigen groups, there was a gradual phase-out of the broad categories and phase-in of the split categories over the transplant years included in the study. For these groups, broad categories were excluded, and split categories were included for transplants occurring on or after the year at which roughly two-thirds (67%) of the phase-in of the split category had been achieved.

We compared DLBCL risk among transplant recipients to that of the general population by calculating a standardized incidence ratio (SIR = observed/expected count). Expected counts were obtained by applying general population DLBCL rates to the person-time at risk

among transplant recipients, stratified by sex, age, race/ethnicity, calendar year, and registry. We also used Poisson regression to obtain incidence rate ratios (IRRs) that compared the incidence of DLBCL in relation to categories of HLA mismatch, each HLA antigen (present versus absent), and HLA zygosity (homozygous versus heterozygous). IRRs were adjusted for sex, age at transplant, race/ethnicity, year of transplant, transplanted organ, and transplant number. The impact of time since transplant on the IRRs was also examined. “Early-onset” DLBCL was defined as DLBCL diagnosed within two years following transplantation, and “late-onset” DLBCL occurred after two years. A two-year threshold was chosen based on prior observations that the incidence curves for PTLD and DLBCL as a function of time since transplantation have a natural inflection point at around two years post-transplant.[2,31] As a sensitivity analysis, we also calculated IRRs restricting the cohort to kidney recipients, given that they comprised 77.3% of our analytic cohort. These kidney transplant-specific calculations were also adjusted for panel reactive antibody (PRA) score and donor type (deceased versus living) given the possible influence of these factors on immunosuppression and thus risk for DLBCL. Bonferroni adjustment of the HLA antigen IRRs was done to account for multiple comparisons. All analyses were performed using Proc Genmod in SAS 9.2 (Cary, NC).

Results

Table 1 describes characteristics of the transplant recipient population. We examined 172,231 transplants with 823,542 person-years of follow-up (median 3.8 years). The majority of the cohort (60.9%) was male. A small proportion (7.4%) was under the age of 20 years at transplantation, 9.2% were age 65 and above, and the majority were between the ages of 35 and 64 (65.8%). The population was racially and ethnically diverse, with 41.5% of recipients being non-white. The majority (77.3%) was kidney recipients, and 9% had received a prior transplant. A total of 902 DLBCLs were diagnosed during follow-up after transplantation, corresponding to a 12-fold increased risk compared with the general population (SIR 12.05, 95%CI 11.27–12.86, Table 4).

In the analysis of HLA mismatch, DLBCL risk was not associated with mismatch at the HLA-A or -B loci, alone (Table 2). However, DLBCL risk decreased with decreasing number of DR mismatches (P for trend=0.0149). Compared to recipients who were completely mismatched for HLA-DR (both antigens), DLBCL risk was lower among recipients with a single mismatch (IRR=0.83, P=0.0529) or no mismatches (IRR=0.76, P=0.0165). When all three loci were considered simultaneously, DLBCL risk appeared reduced among recipients with 0 to 5 mismatches (IRRs ranged from 0.67 to 0.84, compared to those who were completely mismatched at all three loci), although the trend was not statistically significant (P=0.0944). Very similar associations were observed for the kidney transplant subset (Supplementary Table 1).

When we examined early- and late-onset DLBCL separately, we observed substantial heterogeneity of the associations with HLA mismatch (Table 3). For early-onset DLBCL, risk was not associated with mismatch at HLA-B, or -DR, or combined A+B+DR. Decreasing number of mismatches at the HLA-A locus appeared to be associated with increasing risk of DLBCL, although the trend was marginal (P=0.0574). In contrast, for late-

onset DLBCL, risk decreased with decreasing number of mismatches at HLA-A (P for trend = 0.0120), -B (P for trend=0.0148), -DR (P for trend = 0.0005), and A+B+DR (P for trend = 0.0003). For HLA-DR specifically, late-onset DLBCL risk was decreased 42% among transplant recipients with no mismatches compared to those with two mismatches. For all loci combined, late-onset DLBCL risk was decreased 60% among transplant recipients with no mismatches compared to those who were completely mismatched over all three loci. Similar associations were observed for the kidney transplant subset, although late-onset DLBCL risk could not be assessed for DR and A+B+DR due to small numbers (Supplemental Table 2). Furthermore, similar associations were observed when a one year threshold was used to differentiate “early” versus “late” DLBCL (data not shown).

The associations between 88 antigen/antigen groups and DLBCL risk were examined (Supplementary Table 3). In Table 4, results are provided for all HLA antigen-DLBCL associations with a P value less than 0.10, ordered by ascending P values and grouped by locus. The Bonferroni-adjusted P value for 88 tests is 0.0006, and none of the antigen associations met this stringent significance criterion. Among the 14 antigens that had a P value < 0.05, 6 also had P value < 0.05 in the analyses restricted to kidney recipients (Supplementary Table 4). The most notable associations included B38 antigen, which was associated with a 1.48-fold increased risk of DLBCL with the lowest P value (P=0.0061, Table 4). Expression of the C12 antigen was associated with the largest departure from the null association with DLBCL (IRR=1.94, P=0.0337). Also, the B58 antigen was associated with a strong reduced DLBCL risk (IRR=0.47), with the second lowest P value (P=0.0071). The DR13 antigen, which was the strongest candidate antigen in this study based on prior studies,[17,18,21,32,33] was associated with a reduced DLBCL risk (IRR=0.74, P=0.0144).

Finally, DLBCL risk was not associated with zygosity at any HLA locus (Table 5). Stratification of the HLA antigen or zygosity associations by early versus late-onset DLBCL did not reveal notable differences in IRRs (data not shown).

Discussion

To our knowledge, this is the first large-scale, population-based study of HLA and DLBCL risk following solid organ transplantation. We observed that transplant recipients who were matched to their donors for HLA-DR, had a 24% significantly decreased risk of DLBCL compared to mismatched recipients, which may reflect less intensive immunosuppression or lower levels of antigenic stimulation with better matching. Furthermore, we observed heterogeneity in the association between HLA mismatch and DLBCL risk by time since transplantation: a higher degree of matching at HLA-A, -B, -DR, and A+B+DR was significantly associated with a lower risk of late-onset DLBCL, but not early-onset DLBCL, consistent with differences in etiology. Additionally, we observed associations for a number of specific recipient HLA antigens in HLA-A, -B, -C, -DR, and –DQ with DLBCL risk, suggesting the importance of host-specific immune responsiveness to DLBCL-related antigens.

Results from studies evaluating the association between HLA mismatch and post-transplant outcomes related to lymphoid malignancies have been inconsistent. Most studies with

adequate sample sizes have been based in kidney transplant registries. In Australia and New Zealand, HLA mismatch was not associated with post-transplant lymphoproliferative disorder (PTLD, a spectrum of lymphoid cell proliferations including DLBCL) in about 16,000 kidney transplant recipients.[34] On the other hand, two larger studies from the U.S. and France reported that HLA mismatch overall was associated with increased PTLD risk, but did not examine associations with individual HLA loci.[35,36] In a still larger study, including about 153,000 kidney transplant recipients, HLA-DR and HLA-B mismatches were associated with increased NHL risk.[37] The association with HLA-DR mismatch was strikingly more pronounced for NHLs occurring in the kidney,[37] and higher HLA-DR mismatch was associated with increased immunsuppression, including requirement for rejection treatment during the first year, use of T-cell–depleting antibodies for rejection treatment, and high dose of maintenance medications for up to 3 years.[37] PTLD and NHL are heterogeneous entities, and some of the differences among prior studies and our results may reflect differences in the outcomes that were assessed or the substantially larger size of our study.

Our finding that HLA mismatch was most important as a risk factor for late onset DLBCL is open to several interpretations. One possibility is that mismatch leads to increased immune reactivity which necessitates intensified immunosuppressive treatment, resulting in decreased ability for the immune system to control EBV-infected B cells and EBV-driven lymphomagenesis. Our observation that HLA matching is protective for late, but not early, DLBCL, may be explained by the fact that intense immunosuppression is experienced by all transplant recipients in the first few years and tapers in the later years. Thus the differences in immunosuppression related to HLA mismatch may only become apparent in the later years.. Interestingly, in prior research based in the TCM Study, HLA mismatch has not been a significant factor in determining risk for other infection-related cancers, including human papillomavirus associated cancers,[32] Burkitt lymphoma,[38] plasma cell neoplasms,[39] or Kaposi's sarcoma,[40] suggesting that HLA mismatch may be more than a marker for immune suppression in this study of DLBCL. Another possibility is that mismatch causes chronic antigenic stimulation by the allograft, contributing to chronic B-cell activation, thereby increasing the gradual acquisition of lymphomagenic molecular lesions. This notion is supported by data suggesting that EBV is less critical to the development of late DLBCLs.[2]

After correcting for multiple comparisons, no associations with specific HLA antigens remained statistically significant in our analyses. However, several associations that did not meet this stringent significance level are still worth discussing. The most remarkable was with HLA-B38, which was associated with a 1.48-fold increased risk of DLBCL (P=0.0061). In a small previous study, B38 was associated with a 4-fold increase in risk for EBV-positive PTLD (P=0.0004).[41] B38, for which there are at least 16 allelic variants,[42] is a "sister" split category of B39 (both from the broad category B16) which we did not find to be associated with DLBCL (IRR=0.85, P=0.3392). The consistency of our finding with the prior report on PTLD argues against the possibility that this is a chance finding, particularly in light of the fact that HLA-B is the most diverse HLA locus, constituting more than half (nearly 2,000) of the distinct HLA class I molecules.[30]

Among individual class II antigens, DR13 was associated with a notable 26% decreased risk of DLBCL (P=0.0144). DR13 has more than 50 allelic variants, many of which are extremely rare. Accumulating data suggest that DR13 has an important role in immunity to oncoviruses. In a previous study of human papillomavirus-associated cancers that also used data from the TCM Study, Madeleine et al. reported that the DR13 antigen was significantly associated with a reduced risk of cervical and vulvar cancers.[32] Similar protective associations have been observed in immunocompetent populations between allelic variants DRB1*13:01 and DRB1*13:02 and cervical neoplasia.[17,18] Additionally, among immunocompetent people, carriership of DRB1*13:01, *13:02, or *13:03 is associated with decreased risk of NHL, mainly for follicular lymphoma rather than DLBCL.[21,33] Some of the associations that we observed between individual HLA antigens and DLBCL may reflect the complex relationship between EBV and HLA. EBV epitopes are targeted by EBV-specific cytotoxic lymphocytes in an HLA-restricted manner.[43,44] It is plausible that HLA type influences this interaction and thus the immune regulation of EBV. HLA variants may also affect the efficiency of immune surveillance for non-viral tumor antigens. Given the highly polymorphic nature of HLA, and strong linkage disequilibrium patterns across the region, it is also possible that these associations reflect contributions of other genes to the development of transplant-associated DLBCL.

We did not observe an association between HLA zygosity and DLBCL. Heterozygosity at HLA loci has been found to confer an advantage in immune control for infectious diseases, such as HIV, presumably due to the wider array of peptides that can be presented to T-cells.[45] However, in certain situations, homozygosity may actually be beneficial for immune control.[46] Our findings are in contrast to a prior observation that allelic HLA homozygosity was associated with increased DLBCL risk among immunocompetent people.[19]

Because we relied on serologic assessment of HLA, we cannot rule out that we missed some true associations with genetically defined alleles or zygosity. DNA-based methods are becoming common practice in HLA typing laboratories. Nonetheless, serological typing methods have been standardized by the exchange of reagents and cells in the International Histocompatibility Workshops, and the serological equivalencies for genetic variants have been expertly assigned, allowing comparability with genetic data.[42] HLA split categories, resulting from improving specificities of HLA serotyping methods over time, presented an analytic challenge. We erred on the side of maintaining split categories as distinct entities in our analyses due to the possibility that collapsing split categories to harmonize them with the broader categories could mask important differences. However, when the split categories were too rare to examine separately, we analyzed the splits and broads together as a single category, for example, combining A28 (broad), A68 (split), and A69 (split).

An important strength of this study is the examination of DLBCL in more than 170,000 transplants, which allowed us to assess associations with relatively rare HLA antigens. Because we captured DLBCLs arising over an extended period, we were also able to examine associations in different intervals since transplantation. Furthermore, the TCM Study comprises a well-defined, population-based sample of the U.S. transplants, and linkage with cancer registries allowed for complete and uniform cancer ascertainment.

A limitation of this study was the lack of data on long-term immunosuppressive medications. We therefore could not assess whether differences in intensity of immunosuppression mediated the observed associations between HLA mismatch and DLBCL risk. Furthermore, cancer registries do not collect information on tumor EBV status, so we could not stratify risks for EBV-positive and -negative DLBCL. Also, biogeographical ancestry is an important determinant of HLA, and may be associated with DLBCL risk. We adjusted our analyses for self-reported race, but it is possible that some residual confounding remains. Finally, since DLBCLs can arise very late in the post-transplant period, we are likely underestimating the incidence of DLBCLs in our study, particularly if recipients moved out of the cancer registry areas. However, out-migration is uncommon in this population,[29] and we have no reason to believe that the length of follow-up would depend on HLA and cause bias in our results. We included 547,653 person-years of follow-up in the period >2 years post-transplant (twice as much follow-up time as compared to the period ≤2 years), providing a sufficient population from which to estimate DLBCL risk by HLA status in both strata.

In conclusion, these findings suggest that specific subgroups of solid organ transplant recipients may be more susceptible to developing post-transplant DLBCL based on their HLA composition and degree of HLA mismatch with the organ donor. Future studies should aim to define the underlying mechanisms that are responsible for the observed HLA antigen associations. It will also be important to assess the relationship of HLA with control of EBV infection, relative intensity of immunosuppressive therapy, and chronic antigenic stimulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This research was supported in part by the Intramural Research Program of the National Cancer Institute. The authors gratefully acknowledge the support and assistance provided by individuals at the Health Resources and Services Administration (Monica Lin), the SRTR (Paul Newkirk), and the following cancer registries: the states of California, Colorado (Jack Finch), Connecticut (Lou Gonsalves), Georgia (Rana Bayakly), Hawaii (Brenda Hernandez), Iowa, Illinois (Lori Koch), Michigan (Glenn Copeland), New Jersey (Xiaoling Niu), New York (Amy Kahn), North Carolina (Chandrika Rao), Texas (Melanie Williams), and Utah (Janna Harrell), and the Seattle-Puget Sound area of Washington (Margaret Madeleine). We also thank analysts at Information Management Services for programming support (David Castenson, Matthew Chaloux, Michael Curry, Ruth Parsons).

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, Health Resources and Services Administration, SRTR, cancer registries, or their contractors.

The SRTR is currently operated under contract number HHSH250201000018C (Health Resources and Services Administration) by the Minneapolis Medical Research Foundation, Minneapolis, MN. During the initial period when registry linkages were performed, the SRTR was managed by Arbor Research Collaborative for Health in Ann Arbor, MI (contract HHSH234200537009C). The following cancer registries were supported by the SEER Program of the National Cancer Institute: California (contracts HHSN261201000036C, HHSN261201000035C, and HHSN261201000034C), Connecticut (HHSN261201000024C), Hawaii (HHSN261201000037C, N01-PC-35137, and N01-PC-35139), Iowa (HSN261201000032C and N01-PC-35143), New Jersey (HHSN2612013000021I, N01-PC-2013-00021), Seattle-Puget Sound (N01-PC-35142), and Utah (HHSN2612013000171). The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: California (agreement 1U58 DP000807-01), Colorado (U58 DP000848-04), Georgia (5U58DP003875-01), Illinois (5U58DP003883-03), Maryland (U58DP12-1205

3919-03), Michigan (5U58DP003921-03), New Jersey (5U58/DP003931-02), New York (U58DP003879), North Carolina (U58DP000832) and Texas (5U58DP000824-04). Additional support was provided by the states of California, Colorado, Connecticut, Illinois, Iowa, Massachusetts (Massachusetts Cancer Prevention and Control Cooperative Agreement 5458DP003920), New Jersey, New York (including the Cancer Surveillance Initiative), Texas, Utah, and Washington, as well as the University of Utah and Fred Hutchinson Cancer Research Center in Seattle, WA.

Abbreviations (alphabetical list)

CI	confidence intervals
DLBCL	diffuse large B cell lymphoma
EBV	Epstein–Barr virus
HLA	human leukocyte antigens
IRR	incidence rate ratios
NHL	non-Hodgkin lymphoma
PRA	panel reactive antibody
PTLD	post-transplant lymphoproliferative disorder
SRTR	Scientific Registry of Transplant Recipients
SIR	standardized incidence ratio
TCM	Transplant Cancer Match

References

1. Clarke CA, Morton LM, Lynch C, et al. Risk of lymphoma subtypes after solid organ transplantation in the United States. British Journal of Cancer. Jul; 2013 109(1):280–288. [PubMed: 23756857]
2. Gibson TM, Engels EA, Clarke CA, Lynch CF, Weisenburger DD, Morton LM. Risk of diffuse large B-cell lymphoma after solid organ transplantation in the United States. Am J Hematol. 2014; 3(10): 23726.
3. Vegso G, Hajdu M, Sebestyen A. Lymphoproliferative Disorders After Solid Organ Transplantation-Classification, Incidence, Risk Factors, Early Detection and Treatment Options. Pathology & Oncology Research. Sep; 2011 17(3):443–454. [PubMed: 21193979]
4. Kauffman HM, Cherikh WS, McBride MA, Cheng YL, Hanto DW. Post-transplant de novo malignancies in renal transplant recipients: the past and present. Transplant International. Aug; 2006 19(8):607–620. [PubMed: 16827677]
5. Fernberg P, Edgren G, Adami J, et al. Time Trends in Risk and Risk Determinants of Non-Hodgkin Lymphoma in Solid Organ Transplant Recipients. American Journal of Transplantation. Nov; 2011 11(11):2472–2482. [PubMed: 21883909]
6. Farrugia D, Mahboob S, Cheshire J, et al. Malignancy-related mortality following kidney transplantation is common. Kidney International. Jun; 2014 85(6):1395–1403. [PubMed: 24257690]
7. Na R, Grulich AE, Meagher NS, McCaughan GW, Keogh AM, Vajdic CM. De novo Cancer-Related Death in Australian Liver and Cardiothoracic Transplant Recipients. American Journal of Transplantation. May; 2013 13(5):1296–1304. [PubMed: 23464511]
8. Morscio J, Dierickx D, Tousseyn T. Molecular Pathogenesis of B-Cell Posttransplant Lymphoproliferative Disorder: What Do We Know So Far? Clinical & Developmental Immunology. 2013; :13. Article ID 150835. doi: 10.1155/2013/150835

9. Morscio J, Dierickx D, Ferreiro JF, et al. Gene expression profiling reveals clear differences between EBV-positive and EBV-negative posttransplant lymphoproliferative disorders. Am J Transplant. 2013; 13(5):1305–1316. [PubMed: 23489474]
10. Trowsdale J, Campbell RD. Complexity in the Major Histocompatibility Complex. Eur J Immunogenet. Feb-Apr;1992 19(1–2):45–55. [PubMed: 1567814]
11. Patel R, Terasaki PI. Significance of Positive Crossmatch Test in Kidney Transplantation. New England Journal of Medicine. 1969; 280(14):735–&. 1969. [PubMed: 4886455]
12. Peltz M, Edwards LB, Jessen ME, Torres F, Meyer DM. HLA mismatches influence lung transplant recipient survival, bronchiolitis obliterans and rejection: Implications for donor lung allocation. Journal of Heart and Lung Transplantation. Apr; 2011 30(4):426–434. [PubMed: 21145259]
13. Muro M, Lopez-Alvarez MR, Campillo JA, et al. Influence of human leukocyte antigen mismatching on rejection development and allograft survival in liver transplantation: Is the relevance of HLA-A locus matching being underestimated? Transplant Immunology. Mar; 2012 26(2–3):88–93. [PubMed: 22129495]
14. Ansari D, Bucin D, Nilsson J. Human leukocyte antigen matching in heart transplantation: systematic review and meta-analysis. Transpl Int. 2014; 27(8):793–804. [PubMed: 24725030]
15. Dorak MT, Yee LJ, Tang JM, et al. HLA-B,-DRB1/3/4/5, and-DQB1 gene polymorphisms in human immunodeficiency virus-related Kaposi's sarcoma. Journal of Medical Virology. Jul; 2005 76(3):302–310. [PubMed: 15902698]
16. Masala MV, Carcassi C, Cottoni F, Mulargia M, Contu L, Cerimele D. Classic Kaposi's sarcoma in Sardinia: HLA positive and negative associations. International Journal of Dermatology. Sep; 2005 44(9):743–745. [PubMed: 16135142]
17. Madeleine MM, Johnson LG, Smith AG, et al. Comprehensive analysis of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci and squamous cell cervical cancer risk. Cancer Research. May; 2008 68(9):3532–3539. [PubMed: 18451182]
18. Wang SS, Wheeler CM, Hildesheim A, et al. Human Leukocyte Antigen Class I and II Alleles and Risk of Cervical Neoplasia: Results from a Population-Based Study in Costa Rica. J Infect Dis. Nov 15; 2001 184(10):1310–1314. 2001. [PubMed: 11679920]
19. Wang SS, Abdou AM, Morton LM, et al. Human leukocyte antigen class I and II alleles in non-Hodgkin lymphoma etiology. Blood. 2010; 115(23):4820–4823. [PubMed: 20385791]
20. Wang SS, Menashe I, Cerhan JR, et al. Variations in chromosomes 9 and 6p21.3 with risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2011; 20(1):42–49. [PubMed: 21148756]
21. Smedby KE, Foo JN, Skibola CF, et al. GWAS of follicular lymphoma reveals allelic heterogeneity at 6p21.32 and suggests shared genetic susceptibility with diffuse large B-cell lymphoma. PLoS Genet. 2011; 7(4):21.
22. Wang SS, Lu Y, Rothman N, et al. Variation in effects of non-Hodgkin lymphoma risk factors according to the human leukocyte antigen (HLA)-DRB1*01:01 allele and ancestral haplotype 8.1. Plos One. 2011; 6(11):9.
23. Cerhan JR, Fredericksen ZS, Novak AJ, et al. A two-stage evaluation of genetic variation in immune and inflammation genes with risk of non-Hodgkin lymphoma identifies new susceptibility locus in 6p21.3 region. Cancer Epidemiol Biomarkers Prev. 2012; 21(10):1799–1806. [PubMed: 22911334]
24. Cerhan JR, Berndt SI, Vijai J, et al. Genome-wide association study identifies multiple susceptibility loci for diffuse large B cell lymphoma. Nat Genet. 2014; 46(11):1233–1238. [PubMed: 25261932]
25. Bassig BA, Cerhan JR, Au WY, et al. Genetic susceptibility to diffuse large B-cell lymphoma in a pooled study of three Eastern Asian populations. Eur J Haematol. 2015; 22(10):12513.
26. Pourfarziani V, Einollahi B, Taheri S, Nemati E, Nafar M, Kalantar E. Associations of Human Leukocyte Antigen (HLA) haplotypes with risk of developing lymphoproliferative disorders after renal transplantation. Annals of Transplantation. Oct-Dec;2007 12(4):16–22. [PubMed: 18344933]

27. Wheless SA, Gulley ML, Raab-Traub N, et al. Post-transplantation Lymphoproliferative Disease Epstein-Barr Virus DNA Levels, HLA-A3, and Survival. American Journal of Respiratory and Critical Care Medicine. Nov; 2008 178(10):1060–1065. [PubMed: 18755927]
28. Subklewe M, Marquis R, Choquet S, et al. Association of human leukocyte antigen haplotypes with posttransplant lymphoproliferative disease after solid organ transplantation. Transplantation. 2006; 82(8):1093–1100. [PubMed: 17060859]
29. Engels EA, Pfeiffer RM, Fraumeni JF, et al. Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients. Jama-Journal of the American Medical Association. Nov; 2011 306(17): 1891–1901.
30. Goulder PJR, Walker BD. HIV and HLA Class I: An Evolving Relationship. Immunity. Sep; 2012 37(3):426–440. [PubMed: 22999948]
31. Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. American Journal of Hematology. Feb; 2011 86(2):206–209. [PubMed: 21264909]
32. Madeleine MM, Finch JL, Lynch CF, Goodman MT, Engels EA. HPV-Related Cancers After Solid Organ Transplantation in the United States. American Journal of Transplantation. Dec; 2013 13(12):3202–3209. [PubMed: 24119294]
33. Wang SS, Abdou AM, Morton LM, et al. Human leukocyte antigen class I and II alleles in non-Hodgkin lymphoma etiology. Blood. Jun; 2010 115(23):4820–4823. [PubMed: 20385791]
34. Faull RJ, Hollett P, McDonald SP. Lymphoproliferative disease after renal transplantation in Australia and New Zealand. Transplantation. Jul 27; 2005 80(2):193–197. [PubMed: 16041263]
35. Caillard S, Dharnidharka V, Agodoa L, Bohen E, Abbott K. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation. Nov 15; 2005 80(9):1233–1243. [PubMed: 16314791]
36. Caillard S, Lamy FX, Quelen C, et al. Epidemiology of Posttransplant Lymphoproliferative Disorders in Adult Kidney and Kidney Pancreas Recipients: Report of the French Registry and Analysis of Subgroups of Lymphomas. American Journal of Transplantation. Mar; 2012 12(3): 682–693. [PubMed: 22226336]
37. Opelz G, Dohler B. Impact of HLA Mismatching on Incidence of Posttransplant Non-Hodgkin Lymphoma After Kidney Transplantation. Transplantation. Mar; 2010 89(5):567–572. [PubMed: 20110857]
38. Mbulaiteye SM, Clarke CA, Morton LM, et al. Burkitt lymphoma risk in US solid organ transplant recipients. American Journal of Hematology. Apr; 2013 88(4):245–250. [PubMed: 23386365]
39. Engels EA, Clarke CA, Pfeiffer RM, et al. Plasma Cell Neoplasms in US Solid Organ Transplant Recipients. American Journal of Transplantation. Jun; 2013 13(6):1523–1532. [PubMed: 23635036]
40. Mbulaiteye SM, Engels EA. Kaposi's sarcoma risk among transplant recipients in the United States (1993–2003). International Journal of Cancer. Dec; 2006 119(11):2685–2691. [PubMed: 16929513]
41. Reshef R, Luskin MR, Kamoun M, et al. Association of HLA Polymorphisms with Post-transplant Lymphoproliferative Disorder in Solid-Organ Transplant Recipients. American Journal of Transplantation. Apr; 2011 11(4):817–825. [PubMed: 21401872]
42. Holdsworth R, Hurley CK, Marsh SG, et al. The HLA dictionary 2008: a summary of HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1 alleles and their association with serologically defined HLA-A, -B, -C, -DR, and -DQ antigens. Tissue Antigens. 2009; 73(2):95–170. [PubMed: 19140825]
43. Rickinson AB, Moss DJ. Human cytotoxic T lymphocyte responses to Epstein-Barr virus infection. Annual Review of Immunology. 1997; 15:405–431. 1997.
44. Subklewe M, Chahroudi A, Bickharn K, et al. Presentation of Epstein-Barr virus latency antigens to CD8(+), interferon-gamma-secreting, T lymphocytes. European Journal of Immunology. Dec; 1999 29(12):3995–4001. [PubMed: 10602009]
45. Carrington M, Nelson GW, Martin MP, et al. HLA and HIV-1: Heterozygote advantage and B*35-Cw*04 disadvantage. Science. Mar 12; 1999 283(5408):1748–1752. [PubMed: 10073943]

46. Flores-Villanueva PO, Yunis EJ, Delgado JC, et al. Control of HIV-1 viremia and protection from AIDS are associated with HLA-Bw4 homozygosity. Proceedings of the National Academy of Sciences of the United States of America. Apr 24; 2001 98(9):5140–5145. [PubMed: 11309482]

Table 1

Characteristics of 172,231 solid organ transplant recipients, U.S. 1987–2010

	N	%
Sex		
Female	67,409	39.1
Male	104,822	60.9
Age at transplant, years		
0–19	12,772	7.4
20–34	30,266	17.6
35–49	54,635	31.7
50–64	58,732	34.1
65+	15,826	9.2
Race/ethnicity		
White, non-Hispanic	100,800	58.5
Black, non-Hispanic	35,058	20.4
Hispanic	26,916	15.6
Asian/Pacific Islander	9,457	5.5
Year of transplant		
1987–1992	16,086	9.3
1993–1998	44,372	25.8
1999–2004	56,553	32.8
2005–2010	55,220	32.1
Transplanted organ		
Kidney (deceased donor)	85,307	49.5
Kidney (living donor)	47,924	27.8
Heart	19,533	11.3
Pancreas or kidney-pancreas	9,890	5.7
Lung	8,494	4.9
Other/multiple	1,083	0.6
Transplant number		
1	156,690	91.0
2+	15,541	9.0
Panel reactive antibody score		
Missing	30,912	–
0	66,088	46.8
1–79	64,937	46.0
80+	10,294	7.3

Table 2

Associations between HLA mismatch and diffuse large B-cell lymphoma

Antigen	Mismatch number	Transplant recipients with DLBCL	Transplant recipients without DLBCL	SIR	IRR[a]	95% CI	P for trend
		n (%)	n (%)				
Total cohort		**902**	**171,329**	**12.05**			
A	0	169 (18.74)	33,474 (19.54)	11.47	0.93	(0.74–1.16)	0.5088
	1	388 (43.02)	73,007 (42.61)	12.07	0.95	(0.79–1.15)	
	2	340 (37.69)	63,757 (37.21)	12.41	1.00	reference	
B	0	124 (13.75)	26,298 (15.35)	10.24	0.89	(0.70–1.11)	0.3658
	1	333 (36.92)	62,410 (36.43)	11.81	1.01	(0.84–1.22)	
	2	440 (48.78)	81,524 (47.58)	12.95	1.00	reference	
DR	0	151 (16.74)	34,095 (19.90)	9.85	0.76	(0.61–0.95)	0.0149
	1	396 (43.90)	78,388 (45.75)	11.53	0.83	(0.69–1.00)	
	2	339 (37.58)	57,221 (33.40)	13.98	1.00	reference	
A+B+DR	0	60 (6.65)	14,632 (8.54)	9.54	0.67	(0.47–0.95)	0.0944
	1	39 (4.32)	7,406 (4.32)	10.96	0.70	(0.46–1.05)	
	2	96 (10.64)	16,828 (9.82)	12.32	0.69	(0.50–0.97)	
	3	153 (16.96)	32,455 (18.94)	10.43	0.69	(0.52–0.94)	
	4	213 (23.61)	36,777 (21.47)	12.94	0.84	(0.64–1.13)	
	5	209 (23.17)	40,850 (23.84)	12.18	0.67	(0.49–0.90)	
	6	128 (14.19)	21,504 (12.55)	15.01	1.00	reference	

DLBCL=Diffuse large B-cell lymphoma; SIR=Standardized incidence ratio; IRR=Incidence rate ratio

[a]IRRs were calculated as the ratio of incidence rates between each category of mismatch and the reference mismatch category, and were adjusted for sex, age at transplant, race/ethnicity, year of transplant, transplanted organ, and transplant number.

Table 3

Associations between HLA mismatch and early- and late-onset diffuse large B-cell lymphoma

		Early-onset DLBCL (≤ 2 years after transplantation)			Late-onset DLBCL (> 2 years after transplantation)		
Antigen	**Mismatch number**	**IRR[a]**	**95% CI**	**P for trend**	**IRR[a]**	**95% CI**	**P for trend**
A	0	1.38	(0.99–1.92)	0.0574	0.68	(0.59–0.77)	0.0120
	1	1.12	(0.83–1.51)		0.84	(0.76–0.94)	
	2	1.00	reference		1.00	reference	
B	0	1.27	(0.90–1.78)	0.1352	0.67	(0.58–0.76)	0.0148
	1	1.19	(0.89–1.59)		0.90	(0.81–0.99)	
	2	1.00	reference		1.00	reference	
DR	0	1.07	(0.76–1.49)	0.7224	0.58	(0.51–0.66)	0.0005
	1	0.94	(0.70–1.26)		0.76	(0.68–0.84)	
	2	1.00	reference		1.00	reference	
A+B+DR	0	1.17	(0.70–1.94)	0.1155	0.40	(0.32–0.50)	0.0003
	1	1.31	(0.71–2.35)		0.43	(0.34–0.55)	
	2	0.96	(0.56–1.65)		0.55	(0.45–0.66)	
	3	0.92	(0.58–1.48)		0.56	(0.47–0.66)	
	4	0.99	(0.64–1.58)		0.73	(0.62–0.86)	
	5	0.76	(0.48–1.22)		0.60	(0.45–0.80)	
	6	1.00	reference		1.00	reference	

DLBCL=Diffuse large B-cell lymphoma; IRR=Incidence rate ratio

[a]IRRs were calculated as the ratio of incidence rates between each category of mismatch and the reference mismatch category, and were adjusted for sex, age at transplant, race/ethnicity, year of transplant, transplanted organ, and transplant number.

Table 4

Top associations between HLA antigens and diffuse large B-cell lymphoma

Antigen	Transplant recipients with DLBCL	Transplant recipients without DLBCL	SIR	IRR[a]	95% CI	P value
	n (%)	n (%)				
Total cohort	**902**	**171,329**	**12.05**			
HLA-A						
A28 + A68 + A69	115 (12.75)	20,160 (11.77)	14.11	1.30	(1.06–1.58)	0.0099
A03	232 (25.72)	35,116 (20.50)	14.10	1.22	(1.05–1.42)	0.0099
A32	36 (3.99)	8,876 (5.18)	8.43	0.68	(0.48–0.94)	0.0255
A25	18 (2.00)	4,491 (2.62)	7.91	0.67	(0.4–1.03)	0.0911
HLA-B						
B38	53 (5.88)	6,680 (3.90)	16.67	1.48	(1.10–1.93)	0.0061
B58	13 (1.44)	7,405 (4.32)	5.13	0.47	(0.26–0.78)	0.0071
B18	100 (11.09)	14,613 (8.53)	14.87	1.28	(1.03–1.57)	0.0210
B48	2 (0.22)	2,000 (1.17)	2.79	0.23	(0.04–0.72)	0.0388
B55	15 (1.66)	4,177 (2.44)	7.56	0.58	(0.34–0.94)	0.0396
B41	10 (1.11)	3,642 (2.13)	5.99	0.53	(0.27–0.94)	0.0482
B70 + B71 + B72	37 (4.10)	8,343 (4.87)	13.45	1.40	(0.97–1.95)	0.0584
B63	7 (0.78)	3,109 (1.81)	5.45	0.52	(0.22–1.01)	0.0870
B07	195 (21.62)	31,070 (18.13)	13.54	1.15	(0.97–1.34)	0.0954
HLA-C						
C08	21 (2.33)	8,035 (4.69)	6.49	0.56	(0.35–0.85)	0.0098
C12	11 (1.22)	2,245 (1.31)	20.16	1.94	(0.99–3.40)	0.0337
C03 + C09 + C10	125 (13.86)	27,215 (15.88)	10.60	0.81	(0.66–0.98)	0.0340
HLA-DQ						
DQ07	98 (15.86)	29,725 (20.88)	7.97	0.77	(0.59–0.99)	0.0481
DQ08[b]	64 (10.36)	15,031 (10.56)	12.78	1.33	(0.97–1.78)	0.0678
DQ05[b]	92 (14.89)	22,526 (15.82)	11.52	1.25	(0.95–1.63)	0.0968
HLA-DR						
DR13[b]	96 (15.53)	29,321 (20.60)	8.76	0.74	(0.57–0.93)	0.0144

Antigen	Transplant recipients with DLBCL	Transplant recipients without DLBCL	SIR	IRR[a]	95% CI	P value
	n (%)	n (%)				
Total cohort	**902**	**171,329**	**12.05**			
DR17[b]	112 (18.12)	22,562 (15.85)	13.76	1.23	(0.96–1.56)	0.0947

DLBCL=Diffuse large B-cell lymphoma; SIR=Standardized incidence ratio; IRR=Incidence rate ratio

[a]IRRs were calculated as the ratio of incidence rates between each antigen category and all other antigens combined, and were adjusted for sex, age at transplant, race/ethnicity, year of transplant, transplanted organ, and transplant number.

[b]This category includes restricted transplant years reflecting when the split antigen category was in common use (described in supplementary materials).

Table 5

Associations between HLA zygosity and diffuse large B-cell lymphoma

Antigen	Zygosity	Transplant recipients with DLBCL	Transplant recipients without DLBCL	SIR	IRR[a]	95% CI	P value
		n (%)	n (%)				
A	Heterozygous	771 (85.48)	146,613 (85.57)	12.06	1.00	reference	
	Homozygous	130 (14.41)	24,526 (14.32)	12.04	0.95	(0.75–1.18)	0.6363
B	Heterozygous	822 (91.13)	156,972 (91.62)	11.99	1.00	reference	
	Homozygous	79 (8.76)	14,161 (8.27)	12.83	1.09	(0.82–1.43)	0.5365
C	Heterozygous	277 (30.71)	61,742 (36.04)	11.12	1.00	reference	
	Homozygous	270 (29.93)	47,970 (28.00)	12.06	1.00	(0.82–1.23)	0.9708
DQ	Heterozygous	519 (57.54)	106,082 (61.92)	11.34	1.00	reference	
	Homozygous	217 (24.06)	39,244 (22.91)	12.07	0.99	(0.81–1.19)	0.8915
DR	Heterozygous	759 (84.15)	146,386 (85.44)	11.93	1.00	reference	
	Homozygous	133 (14.75)	24,285 (14.17)	12.31	0.99	(0.79–1.24)	0.9541

DLBCL=Diffuse large B-cell lymphoma; SIR=Standardized incidence ratio; IRR=Incidence rate ratio

[a]IRRs were calculated as the ratio of incidence rates between homozygous versus heterozygous (reference) antigen carriers, and were adjusted for sex, age at transplant, race/ethnicity, year of transplant, transplanted organ, and transplant number.