HLA Alleles Cw12 and DQ4 in Kidney Transplant Recipients Are Independent Risk Factors for the Development of Posttransplantation Diabetes

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DOI:
10.1097/TXD.0000000000001188

OPEN

HLA Alleles Cw12 and DQ4 in Kidney Transplant Recipients Are Independent Risk Factors for the Development of Posttransplantation Diabetes

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Background. The association between specific HLA alleles and risk for posttransplantation diabetes (PTDM) in a contemporary and multiethnic kidney transplant recipient cohort is not clear. **Methods.** In this single-center analysis, data were retrospectively analyzed for 1560 nondiabetic kidney transplant recipients at a single center between 2007 and 2018, with median follow-up of 33 mo (interquartile range 8–73). HLA typing methodology was by DNA analysis and reported at the resolution required for the national allocation scheme. Diagnosis of PTDM was aligned with International Consensus recommendations. **Results.** PTDM developed in 231 kidney transplant recipients. Exploring 99 HLA alleles, the presence of Cw12, B52, B38, B58, DQ4, A80, and DR13 and the absence of DQ3 and DR04 were associated with significant increases in PTDM risk. In a multivariable Cox regression model, adjusting for other clinical risk factors for PTDM, the presence of Cw12 (hazard ratio [HR], 1.57; 95% CI, 1.08-2.27; $P = 0.017$) and DQ4 (HR, 1.78; 95% CI, 1.07-2.96; $P = 0.026$) were found to be independent risk factors for PTDM. There was also evidence that the presence of B58 increases PTDM risk within the subgroup of recipients of White ethnicity (HR, 5.01; 95% CI, 2.20-11.42; $P < 0.001$). **Conclusion.** Our data suggest that specific HLA alleles can be associated with PTDM risk, which can be used pretransplantation for PTDM risk stratification. However, association is not causality, and this work requires replication and further investigation to understand underlying biological mechanisms.

(*Transplantation Direct* 2021;00: e00; doi: 10.1097/TXD.0000000000001188. Published online 23 July, 2021.)

INTRODUCTION

Posttransplantation diabetes mellitus (PTDM) is a common complication after kidney transplantation, affecting up to a third of solid organ recipients, and is associated with adverse outcomes.[1] International Consensus guidelines recommend identifying transplant candidates at risk for PTDM to aid patient counseling and risk stratification strategies based upon underlying risk factors.[2] Many risk factors have been identified for the development of PTDM, including those that are both modifiable and nonmodifiable, as well as generic and transplant specific,[3] with new etiological factors continuing to be identified. However, one commonly cited risk factor, which has weak evidence for an underlying etiological link, is specific HLA alleles.

Received 28 April 2021.

Accepted 17 May 2021.

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The authors declare no funding or conflicts of interest.

All authors participated in conception or design, or analysis and interpretation of data, or both. N.P. and A.S. participated in drafting the article or revising it. N.P., A.Z., A.C., F.E., and S.G. did data extraction. N.P., J.H., and A.S. participated in statistical analysis/support. D.B. and A.S. provided intellectual content of critical importance to the work described. All authors did final approval of the version to be published.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplemental Digital Content; http://links.lww.com/TXD/A347

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001188

Although HLA genes have a major impact on risk for type 1 diabetes (contributing to approximately 50% of risk),[4] the heritable contribution to type 2 diabetes is more complex, with confounding from familial and environmental factors.[5] Other types of diabetes have also been shown to have a degree of heritability, including maturity-onset diabetes of the young (MODY)[6] and gestational diabetes.[7] Genetic predisposition for the development of PTDM has been demonstrated in a systematic review and meta-analysis of published studies.[8] Although 3 candidate genes were cited by Benson and colleagues as contributing to the development of PTDM,[8] the heritability of PTDM lacks clear definition and understanding. The pathophysiology of PTDM is distinct from type 1 or 2 diabetes, justifying its separate pathophysiological consideration from other forms of diabetes.[1] Underlying biological mechanisms linking HLA molecules to the development of PTDM are speculative but may include mediation of pathogenetic immune mechanisms which, under the additional influence of special major histocompatibility complex genes of class I and III, lead to diabetes.[9]

Although genome-wide association studies are not readily available at the time of kidney transplantation to guide decision making, HLA typing is known in advance and is easily accessible. Previous studies have linked the development of PTDM to specific HLA alleles, but the evidence base is weak and contradictory.[10-20] These heterogeneous reports (see summary overview in Table 1) have several methodological limitations, with the majority being historical in nature, not using contemporary immunosuppression, and lacking robust definitions of PTDM in line with the latest consensus guidelines.[2] Identifying specific HLA alleles that influence the development of PTDM, which are routinely tested pretransplantation in all kidney transplant candidates, is important as it could facilitate targeted patient counseling and decision making to attenuate risk for PTDM. Therefore, the aim of this study was to explore the link between routinely collected recipient HLA alleles and the risk of PTDM development, after adjustment for known PTDM risk factors, in a large single-center cohort.

MATERIALS AND METHODS

Study Design

We undertook a retrospective cohort analysis of all consecutive kidney-alone transplants performed at a single center in the United Kingdom between January 1, 2007, and June 30, 2018 (with follow-up data to October 13, 2018). Recipients of multiple organs and those with preexisting diabetes were excluded. Data were electronically extracted by the Department of Health Informatics for every study recruit, with manual data linkage to additional electronic patient records. Patient and graft survival outcomes were acquired and linked from NHS Blood and Transplant.

Immunosuppression Protocol

A consistent immunosuppression regimen was initiated throughout the study period, with minimization of tacrolimus exposure, in line with the SYMPHONY protocol.[21] Induction therapy was with basiliximab (20 mg × 2) and methylprednisolone (500 mg). Maintenance therapy included tacrolimus (target 12-h trough level 5–8 ng/L), mycophenolate mofetil (MMF, 2 g daily with tapering to 1 g daily after 6 mo), and corticosteroids tapered to a maintenance low-dose of 5 mg daily.

Diagnosis of PTDM

PTDM was diagnosed in line with the latest Consensus recommendations[2] if any of the following occurred: symptoms of diabetes plus random plasma glucose ≥200 mg/dL (11.1 mmol/L); fasting plasma glucose ≥126 mg/dL (7.0 mmol/L); 2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (rarely undertaken); or HbA1c ≥48 mmol/mol. PTDM was not diagnosed for recipients if only present during the immediate 6-wk postoperative period.

TABLE 1.

HLA alleles and PTDM risk in literature

						HLA alleles and PTDM		
Study	Published	Cohort	Country	Number of cases	Immunosuppression	Associated with increased PTDM risk	No significant association with PTDM	Associated with reduced PTDM risk
Hjelmesaeth	1997	1995–1996	Norway	173	Cyclosporine, azathioprine, steroids	B27	DR3, DR4	
Reddy	2015	2004–2009	India	251	Tacrolimus or cyclosporine, mycophenolate, steroids	B52, A10,[a] B13[b]		A28, DR2,[b] A1
Torres-Romero	2006	1997–2004	Puerto Rico	525	Not known		A3, DR3, DR4, Dr17, DR18	
Sumrani	1991	1983–1988	United States	337	Cyclosporine, steroids	A30, Bw42		
David	1980	1971–1977	United States	286	Azathioprine, steroids	A28	B18, Bw15	
Nafar	2005	1984–2004	Iran	61	Not clearly stated	DR8, A26		DR6, DR52
Mazali	2008	Not stated	Brazil	67	Tacrolimus, mycophenolate, steroids	DR13		
Pietrzak-Nowacka	2010	1988–2005	Poland	196	Variable	B27		
Addous	2000	1989–1997	Saudi Arabia	153	Cyclosporine, azathioprine, steroids		A28, A30, B8, DR3, DR4, B7, DR2	
Bee	2011	1998–2007	Singapore	388	Variable	BR13, BR15		
von Kiparski	1990	1964–1988	Switzerland	901	Cyclosporine, azathioprine, steroids	B8	A28, B15, DR3, DR4, B7, DR2	

[a]Only for patients receiving cyclosporine.
[b]Only for patients receiving tacrolimus.
PTDM, posttransplantation diabetes.

These data were not available for electronic extraction, and therefore, it was done manually through electronic patient record search.

HLA Typing Methodology

All cases were typed by DNA analysis using Lifecodes SSO kits (supplied by Imucor) and reported at the resolution required for the national allocation scheme. HLA alleles were accordingly assigned as serological equivalents.

Definitions of Variables

Baseline and posttransplant data were extracted and classified from our database as follows. The primary variables of interest were specific HLA alleles for the recipient, with a range of HLA alleles examined for class I and II HLA genes. HLA mismatch levels were defined and graded as level 1 (HLA mismatch 0), level 2 (HLA mismatch 0 DR and 0/1 B), level 3 (HLA mismatch 0 DR and 2B, or 1 DR and 0/1 B), and level 4 (1 DR and 2B, or 2 DR). Matchability was calculated from a standardized pool of 10,000 recent donors, from which the numbers of blood group identical donors that recipients are well or favorably HLA-mismatched were counted. This number was converted to a standardized score between 1 and 10, which was used to categorize recipients into 1 of 3 matchability groups; easy (1–3), moderate (4–6), or hard (7–10) to match.

To calculate the follow-up time of each patient, data for patient survival outcomes were acquired from our hospital informatics team, with record linkage to the national death registry. Data for graft survival outcomes were acquired from NHS Blood and Transplant, with record linkage to electronic patient records for validation.

Statistical Analysis

The primary outcome of interest was development of PTDM. Associations between HLA alleles and PTDM were assessed using a time-to-event approach, with the event of interest being PTDM, and patients being censored at death, graft loss, retransplant, or the final follow-up appointment. Univariable Cox regression models were initially used to compare between patients where each allele was present versus absent. Because of the large number of alleles being assessed, the significance of the factors in the resulting models was assessed at both $P < 0.05$ and after Bonferroni correction for 99 comparisons ($P < 0.0005$). All alleles identified as significant at either threshold were then considered for inclusion in a multivariable Cox regression analysis, with a forwards stepwise approach used to produce a parsimonious model.

Alleles selected for inclusion in the parsimonious model of PTDM on the initial analysis were then assessed in further detail. For these, the association with PTDM was visualized using Kaplan–Meier curves, which were used to estimate PTDM rates. The characteristics of recipients were then compared between those with presence versus absence of the alleles, using Mann–Whitney *U* tests for ordinal or continuous variables and Fisher's exact tests for nominal variables.

Univariable Cox regression models were then used to assess the associations between baseline factors and PTDM. These factors were then considered for inclusion in a multivariable Cox regression model, with a backwards stepwise approach used to produce a parsimonious model. To prevent excessive exclusions of cases with missing data in the multivariable analysis, these were replaced with the mean in the case of continuous variables or classified as a separate "missing data" category in the case of categorical variables. A second backwards stepwise procedure was then used to select alleles to be added to the model, with all those found to be significant on previous univariable analysis considered for inclusion.

To assess the interplay between recipient ethnicity and selected alleles, Cox regression models were then produced, with the presence of the allele, recipient ethnicity, and an interaction term as covariates. These were followed by subgroup analyses by recipient ethnicity to quantify the associations between the allele and PTDM for each ethnicity.

All analyses were performed using IBM SPSS 22 (IBM Corp., Armonk, NY), with $P < 0.05$ deemed to be indicative of statistical significance, unless stated otherwise.

Approvals

This study received institutional review board approval (identifier; CARMS-12578). The corresponding author had full access to all data.

RESULTS

Cohort Characteristics

Data were available for a total of N = 1560 transplants, for which donor and recipient characteristics are reported in Table 2. Patients were followed up for a median of 33 mo (interquartile range, 8–73) posttransplant, during which time N = 350 patients were censored for the analysis of PTDM due to death, graft loss, or retransplant. In total, N = 231 patients developed PTDM, giving Kaplan–Meier estimated rates of 12.7%, 19.1%, and 27.4% at 1, 5, and 10 y, respectively (see Figure 1).

Associations Between HLA Alleles and PTDM

Data relating to HLA alleles were recorded in N = 1501 cases, with a total of 99 alleles considered in the analysis, a full list of which is reported in Table 3. Of these, 8 were not observed in any patients in the cohort and so were not considered in subsequent analysis. The prevalence of the remaining alleles ranged widely, from being present in a single patient (A43, B73, and A80; 0.1%) to over half of the cohort (DQ3; 53.2%).

On univariable analysis, a total of N = 9 alleles were found to be significantly associated with PTDM (see Table 3). Of these, only the presence of Cw12 (HR, 2.23; $P < 0.001$) was found to be significantly associated with PTDM using the Bonferroni-corrected threshold of $P < 0.0005$. Using the standard $P < 0.05$ threshold, the presence of B52, B38, B58, DQ4, A80, and DR13, and the absence of DQ3 and DR4 were additionally found to be associated with a significant increase in the risk of PTDM. All of these alleles were then considered for inclusion in a multivariable Cox regression model, using a forwards stepwise approach, to identify those that were independently associated with PTDM. Cw12 remained the strongest predictor of PTDM in this model ($P < 0.001$), with B58 ($P = 0.025$) and DQ4 ($P = 0.031$) also identified as significant.

TABLE 2.

Baseline characteristics of the study cohort

	N	Statistic
Donor factors		
Age (y)	1291	49 (38–58)
Sex (% Male)	1291	654 (50.7%)
Ethnicity	1300	
White		1182 (90.9%)
South Asian		69 (5.3%)
Other		49 (3.8%)
Body mass index (kg/m^2)	758	25.8 (23.4–28.7)
CMV (% positive)	1214	611 (50.3%)
Type	1504	
Living		605 (40.2%)
Donation after brain death		690 (45.9%)
Donation after circulatory death		209 (13.9%)
Donor risk index	991	1.68 (1.36–2.06)
Recipient factors		
Age (y)	1560	47 (36–57)
Sex (% Male)	1560	906 (58.1%)
Ethnicity	1560	
White		1045 (67.0%)
South Asian		281 (18.0%)
Other		234 (15.0%)
Body mass index (kg/m^2)	1517	26.5 (23.5–29.8)
CMV (% positive)	1073	375 (34.9%)
Hepatitis C (% positive)	1506	6 (0.4%)
Polycystic kidney disease	1353	248 (18.3%)
Glomerular causes	1353	411 (30.4%)
Tubulointerstitial causes	1353	142 (10.5%)
Renovascular disease	1353	42 (3.1%)
Hypertension	1353	186 (13.7%)
Other causes	1353	274 (20.3%)
Unknown	1353	50 (3.7%
Dialysis	1386	1061 (76.6%)
Previous transplant	1504	174 (11.6%)
Waiting list time (mo)	1216	29.4 (11.6–54.8)
Matching/transplant factors		
Calculated reaction frequency	1290	
0%		848 (65.7%)
1%–85%		332 (25.7%)
>85%		110 (8.5%)
Matchability	972	
Easy		374 (38.5%)
Moderate		434 (44.7%)
Hard		164 (16.9%)
HLA mismatch	1560	
Level 1		175 (11.2%)
Level 2		415 (26.6%)
Level 3		744 (47.7%)
Level 4		226 (14.5%)
ABO incompatible	1560	77 (4.9%)
Cold ischemic time (h)	1211	11.6 (3.2–17.1)

Data are reported as N (column %), or as median (interquartile range), as applicable.
CMV, cytomegalovirus.

Further Analysis of Cw12, B58, and DQ4

The 3 alleles selected by the forwards stepwise procedure were then analyzed in further detail. Kaplan–Meier curves of the associations between these alleles and PTDM are shown in Figure 2. These returned Kaplan–Meier estimated PTDM rates at 5 y for patients with the allele present versus absent

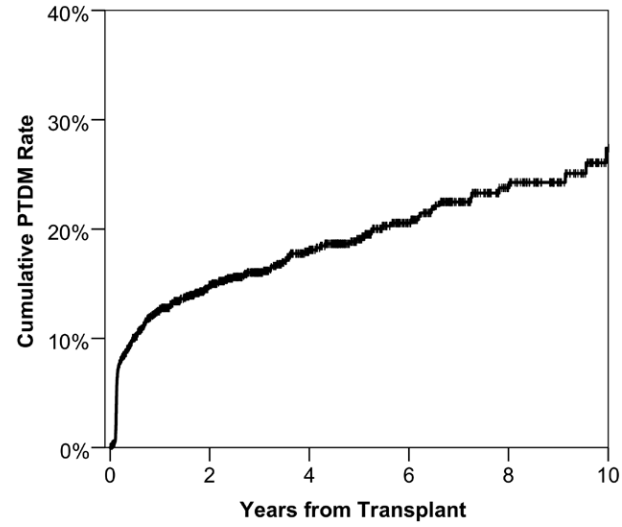

FIGURE 1. Kaplan–Meier curve of PTDM. PTDM, posttransplantation diabetes.

of 35.5% versus 17.3% for Cw12, 33.3% versus 18.4% for B58, and 28.8% versus 18.6% for DQ4.

Analysis of recipient characteristics found all 3 alleles to be significantly associated with the distribution of ethnicity (all $P < 0.001$, see Table 4). In the case of Cw12 and B58, South Asian patients were overrepresented in the present (versus absent) allele groups, making up 48.1% versus 14.7% and 42.6% versus 17.2% of cases, respectively. For DQ4, the "other" ethnicities (ie, neither White nor South Asian) were overrepresented in the present group (34.2% versus 13.9% in the absent group).

Independent Predictors of PTDM

A multivariable model was then produced to identify donor-, recipient-, and transplant-related factors that were independent predictors of PTDM (see Table 5). This identified increasing recipient age (hazard ratio [HR], 1.49 per decade; $P < 0.001$) and BMI (HR, 1.35 per 5 kg/m^2; $P < 0.001$) to be independently associated with a significantly increased PTDM risk. In addition, recipient ethnicity was significantly independently associated with PTDM risk, with HRs of 2.37 ($P < 0.001$) for South Asian recipients, and 1.68 ($P = 0.007$) for other Non-White ethnicities, relative to White recipients. The model additionally selected donor cytomegalovirus positivity ($P = 0.089$) and increasing calculated reaction frequency ($P = 0.090$) for inclusion, although neither reached statistical significance.

The model was then extended to additionally consider the 9 alleles previously identified as significant on univariable analysis (Table 6). Of these, the stepwise procedure identified the presence of Cw12 (HR, 1.57; $P = 0.017$) and DQ4 (HR, 1.78; $P = 0.026$) to be significant independent predictors of PTDM after adjusting for the previously described factors.

Interplay Between Alleles and Recipient Ethnicity

Because recipient ethnicity was found to be significantly associated with both PTDM and the alleles included in the further analysis (Cw12, B58, and DQ4), the interactions between these alleles and ethnicity were assessed (see Table 7). This found no evidence of a significant interaction

TABLE 3.

Prevalence of HLA alleles and univariable analysis of associations with PTDM

HLA Allele	Prevalence	Hazard ratio (95% CI)	*P*	HLA allele	Prevalence	Hazard ratio (95% CI)	*P*
Cw12	158 (10.5%)	2.23 (1.58–3.15)	**<0.001**[a]	B49	42 (2.8%)	1.27 (0.60–2.71)	0.528
B52	63 (4.2%)	2.29 (1.41–3.72)	**<0.001**	A68	132 (8.8%)	1.15 (0.74–1.81)	0.531
B38	25 (1.7%)	2.77 (1.37–5.61)	**0.005**	B37	37 (2.5%)	1.25 (0.59–2.66)	0.558
B58	61 (4.1%)	1.84 (1.10–3.05)	**0.019**	B46	5 (0.3%)	N/A[b]	0.579
DQ3	798 (53.2%)	0.74 (0.56–0.96)	**0.022**	Cw4	263 (17.5%)	0.91 (0.63–1.29)	0.588
DQ4	79 (5.3%)	1.71 (1.04–2.80)	**0.034**	A36	4 (0.3%)	N/A[b]	0.590
A80	1 (0.1%)	N/A[b]	**0.038**	B7	320 (21.3%)	0.91 (0.66–1.27)	0.593
DR4	438 (29.2%)	0.72 (0.53–0.99)	**0.043**	B62	151 (10.1%)	0.89 (0.56–1.40)	0.603
DR13	301 (20.1%)	1.36 (1.00–1.84)	**0.048**	B81	3 (0.2%)	N/A[b]	0.604
Cw16	134 (8.9%)	1.48 (0.99–2.21)	0.057	B41	17 (1.1%)	1.35 (0.43–4.22)	0.607
Cw8	103 (6.9%)	0.54 (0.27–1.04)	0.067	DQ6	642 (42.8%)	0.93 (0.71–1.22)	0.608
B55	63 (4.2%)	0.41 (0.15–1.10)	0.077	A34	10 (0.7%)	0.62 (0.09–4.44)	0.636
DR16	35 (2.3%)	1.73 (0.92–3.27)	0.090	A11	243 (16.2%)	0.92 (0.63–1.33)	0.644
DR8	74 (4.9%)	1.56 (0.93–2.64)	0.095	A1	407 (27.1%)	0.94 (0.69–1.27)	0.690
B60	158 (10.5%)	0.65 (0.39–1.08)	0.098	B75	16 (1.1%)	0.76 (0.19–3.04)	0.694
Cw14	49 (3.3%)	1.66 (0.91–3.05)	0.101	B27	122 (8.1%)	1.09 (0.69–1.73)	0.699
B63	21 (1.4%)	1.92 (0.85–4.32)	0.115	B78	2 (0.1%)	N/A[b]	0.710
A23	64 (4.3%)	1.52 (0.88–2.60)	0.132	DR11	206 (13.7%)	1.07 (0.74–1.55)	0.712
Cw3	369 (24.6%)	0.79 (0.58–1.09)	0.159	DR9	40 (2.7%)	1.15 (0.54–2.45)	0.713
B64	25 (1.7%)	0.25 (0.03–1.77)	0.164	B48	4 (0.3%)	N/A[b]	0.715
Cw1	94 (6.3%)	0.63 (0.32–1.22)	0.169	B61	75 (5.0%)	0.89 (0.47–1.68)	0.718
A32	102 (6.8%)	0.66 (0.36–1.21)	0.175	DR7	340 (22.7%)	0.95 (0.69–1.30)	0.729
Cw05	248 (16.5%)	0.77 (0.52–1.13)	0.176	A66	15 (1.0%)	1.22 (0.39–3.81)	0.733
B51	179 (11.9%)	1.28 (0.88–1.85)	0.191	Cw15	127 (8.5%)	1.08 (0.68–1.70)	0.754
B65	49 (3.3%)	0.52 (0.20–1.41)	0.201	B73	1 (0.1%)	N/A[b]	0.755
DR10	77 (5.1%)	1.39 (0.82–2.35)	0.221	DR18	16 (1.1%)	0.81 (0.20–3.27)	0.770
DR12	58 (3.9%)	0.58 (0.24–1.40)	0.223	Cw17	32 (2.1%)	1.12 (0.46–2.72)	0.801
A24	256 (17.1%)	1.23 (0.88–1.71)	0.227	A2	694 (46.2%)	1.03 (0.79–1.34)	0.803
A3	347 (23.1%)	0.83 (0.60–1.14)	0.252	B45	41 (2.7%)	0.92 (0.41–2.08)	0.849
DQ5	487 (32.4%)	1.16 (0.89–1.53)	0.273	B18	91 (6.1%)	0.95 (0.54–1.66)	0.850
DR15	453 (30.2%)	0.85 (0.64–1.14)	0.278	A43	1 (0.1%)	N/A[b]	0.857
B57	124 (8.3%)	0.76 (0.46–1.26)	0.287	B13	58 (3.9%)	1.05 (0.56–1.98)	0.881
DR1	246 (16.4%)	0.82 (0.56–1.19)	0.300	Cw6	264 (17.6%)	0.98 (0.70–1.36)	0.883
DR103	37 (2.5%)	0.55 (0.18–1.72)	0.306	B8	316 (21.1%)	0.98 (0.71–1.35)	0.892
B71	19 (1.3%)	1.67 (0.62–4.48)	0.312	A25	35 (2.3%)	1.05 (0.47–2.36)	0.911
A29	86 (5.7%)	1.29 (0.77–2.14)	0.329	B47	10 (0.7%)	1.07 (0.26–4.33)	0.923
B56	17 (1.1%)	0.40 (0.06–2.82)	0.355	Cw2	110 (7.3%)	1.02 (0.62–1.68)	0.930
DR14	113 (7.5%)	1.23 (0.78–1.95)	0.373	DR17	379 (25.2%)	1.01 (0.75–1.37)	0.954
B39	**52 (3.5%)**	**1.35 (0.69–2.63)**	**0.378**	A26	110 (7.3%)	1.01 (0.62–1.64)	0.961
B44	384 (25.6%)	0.87 (0.64–1.19)	0.383	B50	19 (1.3%)	1.02 (0.33–3.20)	0.969
DQ2	603 (40.2%)	1.12 (0.86–1.46)	0.393	Cw7	766 (51.0%)	1.00 (0.77–1.30)	0.993
B35	212 (14.1%)	1.16 (0.81–1.67)	0.411	A69	0 (0.0%)	–	–
B42	9 (0.6%)	N/A[b]	0.427	B76	0 (0.0%)	–	–
A30	84 (5.6%)	0.78 (0.43–1.43)	0.427	B77	0 (0.0%)	–	–
B72	13 (0.9%)	1.52 (0.49–4.76)	0.470	B54	0 (0.0%)	–	–
A33	65 (4.3%)	1.26 (0.67–2.38)	0.476	B59	0 (0.0%)	–	–
B53	31 (2.1%)	0.71 (0.27–1.92)	0.505	B67	0 (0.0%)	–	–
Cw18	6 (0.4%)	N/A[b]	0.506	B82	0 (0.0%)	–	–
A74	26 (1.7%)	0.68 (0.22–2.13)	0.508	B83	0 (0.0%)	–	–
A31	87 (5.8%)	1.21 (0.69–2.11)	0.513			–	–

Results are based on the N = 1501 for whom details of HLA alleles were available. The prevalence represents the number and percentage of patients for whom the stated allele was present. Hazard ratios are from Cox regression models, with PTDM as the event of interest, and are reported for the allele present vs. absent. The table is sorted by the resulting *P* value, with bold values being significant at $P < 0.05$.

[a]Remains significant after Bonferroni correction for 99 comparisons ($P < 0.0005$).

[b]The hazard ratio could not be reliably estimated due to the small number of cases in the allele present group.

CI, confidence intervals; PTDM, posttransplantation diabetes.

between recipient ethnicity and either Cw12 ($P = 0.373$) or DQ4 ($P = 0.197$), implying that the associations between these alleles and PTDM were not mediated by ethnicity. However, a significant interaction effect was observed for B58 ($P = 0.004$), which is visualized in Figure 3. Subgroup analysis by recipient ethnicity found no significant association between the

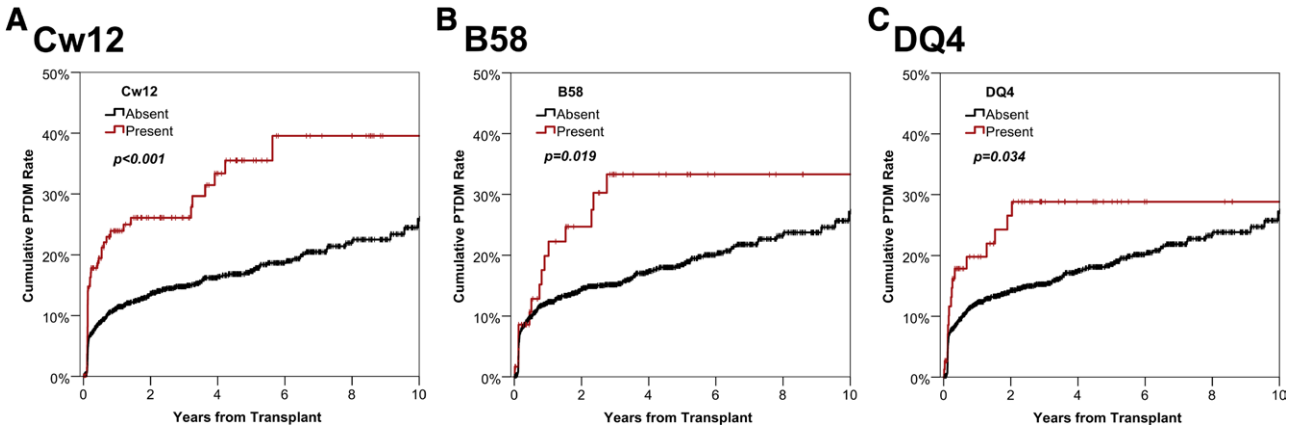

FIGURE 2. Kaplan–Meier curve of PTDM stratified by (A) HLA Cw12, (B) HLA B58, and (C) HLA DQ4 status. PTDM, posttransplantation diabetes.

presence of B58 and PTDM risk for South Asian (HR, 0.58; $P = 0.297$) or Other Non-White (HR, 1.48; $P = 0.381$) ethnicities. However, a significant association was observed in White recipients (HR, 5.01; $P < 0.001$), with Kaplan–Meier estimated PTDM rates at 5 y of 58.7% versus 15.0% for those with present versus absent B58.

DISCUSSION

In this single-center study, we have identified the presence of either Cw12 or DQ4 HLA alleles in kidney transplant recipients as independent risk factors for the development of PTDM. An array of other HLA alleles did not meet statistical significance, either in univariable analysis or after adjustment with baseline clinical variables associated with PTDM. These novel associations have not been previously reported. However, these findings do not necessarily imply causality, and further research is warranted to investigate this association and replicate the findings in other contemporary cohorts.

As shown in Table 1, the association between HLA typing and risk of PTDM is heterogeneously reported in the literature. These small studies are historical, do not use current tacrolimus-based immunosuppression protocol, and have inconsistent diagnostic criteria for PTDM (none compatible with international Consensus recommendations).[2] In addition, the distributions of ethnicity are variable and reflect the diverse prevalence of HLA alleles. For example, previous studies were conducted in diverse cohorts including Norwegian,[11] south Asian,[10] Puerto Rican,[12] United States (majority African-American),[13] United States (majority White),[14] Brazilian,[15] Polish,[16] Saudi Arabian,[17] Singaporean,[18] and Swiss[19] kidney transplant recipients. Because of such heterogeneous data, the original international consensus guidelines from 2003[22] dismissed the reliability of HLA alleles as specific risk factors for PTDM. Although the 2013 guidelines recommended further research for identification of risk factors for PTDM,[2] no specific discussion was made on the issue of HLA alleles.

Our study addresses several of the limitations in the existing literature. It is representative of a large, ethnically diverse kidney transplant cohort receiving contemporary immunosuppression aligned with the SYMPHONY study.[21] As the largest cohort analyzed, it has a lower risk of type 2 statistical errors, which are common issues when investigating a high number

TABLE 4.

Associations between Cw12, B58, and DQ4 and recipient characteristics

	Cw12			B58			DQ4		
	Absent	Present	*P*	Absent	Present	*P*	Absent	Present	*P*
Age (y)	46 (36-57)	49 (37-60)	0.082	47 (36-57)	45 (34-56)	0.765	47 (36-57)	45 (37-55)	0.574
Sex (% male)	793 (59.0%)	84 (53.2%)	0.172	838 (58.2%)	39 (63.9%)	0.427	834 (58.6%)	43 (54.4%)	0.483
Ethnicity			**<0.001**			**<0.001**			**<0.001**
White	942 (70.1%)	62 (39.2%)		990 (68.8%)	14 (23.0%)		968 (68.1%)	36 (45.6%)	
South Asian	197 (14.7%)	76 (48.1%)		247 (17.2%)	26 (42.6%)		257 (18.1%)	16 (20.3%)	
Other	204 (15.2%)	20 (12.7%)		203 (14.1%)	21 (34.4%)		197 (13.9%)	27 (34.2%)	
BMI (kg/m^2)	27 (24-30)	27 (23-29)	0.763	27 (24-30)	26 (24-29)	0.474	27 (24-30)	26 (24-29)	0.431
CMV (% positive)	320 (33.6%)	51 (45.9%)	**0.012**	351 (34.5%)	20 (43.5%)	0.268	349 (34.8%)	22 (37.3%)	0.676
HCV (% positive)	4 (0.3%)	0 (0.0%)	1.000	2 (0.1%)	2 (3.5%)	**0.009**	3 (0.2%)	1 (1.3%)	0.191
PKD	210 (17.9%)	23 (17.0%)	0.906	226 (18.0%)	7 (14.6%)	0.701	223 (18.0%)	10 (14.9%)	0.624
Dialysis	925 (76.4%)	113 (79.0%)	0.531	993 (76.5%)	45 (80.4%)	0.629	986 (77.0%)	52 (71.2%)	0.257
Previous transplant	148 (11.4%)	18 (11.7%)	0.893	160 (11.5%)	6 (10.0%)	1.000	161 (11.7%)	5 (6.5%)	0.198
Waiting list time (mo)	29 (12-55)	34 (14-57)	0.366	29 (11-54)	43 (17-64)	**0.022**	28 (11-54)	38 (15-65)	**0.031**

Data are reported as N (Column %), with *P* from Fisher's exact tests, or as median (interquartile range), with *P* from Mann–Whitney *U* tests, as applicable. Bold *P* are significant at $P < 0.05$.
BMI, body mass index; CMV, cytomegalovirus; HCV, hepatitis C; PKD, polycystic kidney disease.

TABLE 5.

Other factors associated with PTDM

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	***P***	**Hazard ratio (95% CI)**	***P***
Donor factors				
Age (per decade)	1.12 (1.01–1.24)	**0.037**	–	NS
Sex (female)	0.83 (0.63–1.09)	0.178	–	NS
Ethnicity		0.768	–	NS
White	1	-	–	–
South Asian	1.05 (0.57–1.94)	0.866	–	–
Other	0.73 (0.30–1.77)	0.484	–	–
BMI (per 5 kg/m^2)	0.95 (0.79–1.15)	0.613	–	NS
CMV (Positive)	1.46 (1.10–1.93)	**0.008**	1.28 (0.96–1.70)	0.089
Type		**0.006**		
Living	1	-	–	–
DBD	1.48 (1.11–1.99)	**0.009**	–	–
DCD	1.77 (1.20–2.62)	**0.004**	–	–
DRI (per point)	1.52 (1.19–1.94)	**<0.001**	–	NS
Recipient factors				
Age (per decade)	1.46 (1.32–1.61)	**<0.001**	1.49 (1.35–1.66)	**<0.001**
Sex (Female)	1.22 (0.94–1.57)	0.138	–	NS
Ethnicity		**<0.001**	–	**<0.001**
White	1	-	1	-
South Asian	2.13 (1.58–2.87)	**<0.001**	2.37 (1.76–3.21)	**<0.001**
Other	1.51 (1.04–2.18)	**0.030**	1.68 (1.15–2.44)	**0.007**
BMI (per 5 kg/m^2)	1.34 (1.20–1.50)	**<0.001**	1.35 (1.20–1.51)	**<0.001**
CMV (Positive)	1.39 (1.04–1.87)	**0.028**	–	NS
HCV (Positive)	3.22 (0.80–12.96)	0.100	–	NS
PKD	1.23 (0.89–1.71)	0.214	–	NS
Dialysis	1.07 (0.78–1.47)	0.677	–	NS
Previous transplant	0.77 (0.49–1.21)	0.263	–	NS
Waiting list time (per year)	1.04 (0.99–1.10)	0.109	–	NS
Matching/transplant factors				
CRF		**0.024**		0.090
0%	1	-	1	-
1-85%	1.50 (1.11–2.01)	**0.007**	1.43 (1.06–1.92)	0.020
>85%	0.99 (0.57–1.72)	0.972	1.21 (0.69–2.12)	0.501
Matchability		0.775	–	NS
Easy	1	-	–	–
Moderate	0.94 (0.67–1.33)	0.729	–	–
Hard	1.10 (0.71–1.71)	0.670	–	–
HLA mismatch		0.485	–	NS
Level 1	1	-	–	–
Level 2	1.15 (0.70–1.90)	0.582	–	–
Level 3	1.36 (0.85–2.16)	0.197	–	–
Level 4	1.15 (0.67–1.99)	0.614	–	–
ABO incompatible	0.72 (0.38–1.35)	0.306	–	NS
CIT (per h)	1.02 (1.00–1.04)	**0.031**	–	NS

Results are from univariable Cox regression models. Hazard ratios are reported for the stated category, relative to the reference for categorical variables, or for the stated number of units increase for continuous variables. For the univariable analysis, each factor was assessed separately, and cases with missing data were excluded on a per-analysis basis. The multivariable analysis replaced missing values with the mean in the case of continuous variables or considered these as a separate "missing data" category for categorical variables (these categories are not reported in the table). A backwards stepwise approach was then used to produce a parsimonious model. Bold *P* are significant at $P < 0.05$. NS = not selected for inclusion in the model by the stepwise procedure.

–, not significant; BMI, body mass index; CI, confidence intervals; CMV, cytomegalovirus; CRF, calculated reaction frequency; DBD, donor after brain death; DCD, donor after cardiac death; DRI, donor risk index; HCV, hepatitis C; PKD, polycystic kidney disease; PTDM, posttransplantation diabetes.

of HLA alleles in small study populations. Previous studies tended to limit their HLA typing to the A, B, and DR loci, whereas this analysis includes a more comprehensive major histocompatibility complex analysis by including HLA-C and HLA-DQ. In addition, most of the previous studies were unable to undertake multivariable analysis, which is important considering the disparate frequency of certain HLA alleles among specific ethnic groups. For example, although we observed a greater prevalence of HLA-Cw12 and HLA-DQ4 in kidney transplant recipients of south Asian ethnicity, our adjusted analysis and interaction studies confirmed the independent association of both HLA alleles with risk for PTDM. Reddy and colleagues did not observe any similar association in their analysis of South Asian kidney transplant recipients

TABLE 6.

Multivariable analysis of PTDM, including HLA alleles

	Hazard ratio (95% CI)	*P*
Cw12 (present)	1.57 (1.08–2.27)	**0.017**
DQ4 (present)	1.78 (1.07–2.96)	**0.026**
Donor CMV (positive)	1.24 (0.93–1.66)	0.136
Recipient age (per decade)	1.50 (1.35–1.66)	**<0.001**
Recipient ethnicity		**<0.001**
White	1	–
South Asian	2.07 (1.50–2.87)	**<0.001**
Other	1.63 (1.10–2.40)	**0.014**
Recipient BMI (per 5 kg/m^2)	1.35 (1.21–1.52)	**<0.001**
CRF		0.122
0%	1	–
1-85%	1.41 (1.04–1.91)	0.026
>85%	1.26 (0.72–2.21)	0.411

Results are from a multivariable Cox regression analysis. The factors selected for inclusion in the multivariable analysis in Table 5 were initially entered into the model. A backward-stepwise approach was then used to select alleles for inclusion in the model from the subset of N = 9 that were identified as significant on the univariable analysis in Table 3. Bold *P* are significant at $P < 0.05$.

–, not significant; BMI, body mass index; CMV, cytomegalovirus; CRF, calculated reaction frequency; PTDM, posttransplantation diabetes.

TABLE 7.

Associations between alleles and PTDM by recipient ethnicity

	N	Hazard ratio (95% CI)	Interaction *P*
Cw12			0.373
White	1004	2.08 (1.17–3.69)	
South Asian	273	1.41 (0.84–2.37)	
Other	224	3.21 (1.31–7.87)	
Overall	1550	2.23 (1.58–3.15)	
B58			**0.004**
White	1004	5.01 (2.20–11.42)	
South Asian	273	0.58 (0.21–1.61)	
Other	224	1.48 (0.61–3.58)	
Overall	1550	1.84 (1.10–3.05)	
DQ4			0.197
White	1004	2.42 (1.23–4.77)	
South Asian	273	1.44 (0.58–3.59)	
Other	224	0.72 (0.22–2.36)	
Overall	1550	1.71 (1.04–2.80)	

Hazard ratios are for allele present vs. absent and are reported for the cohort as a whole ("overall"), as well as within each subgroup of recipient ethnicity. *P* is from the interaction term of the Cox regression model, with the allele, recipient ethnicity and an interaction as covariates. As such, these represent comparisons between the hazard ratios in the 3 recipient ethnicity subgroups. Bold *P* are significant at $P < 0.05$.

CI, confidence intervals; PTDM, posttransplantation diabetes.

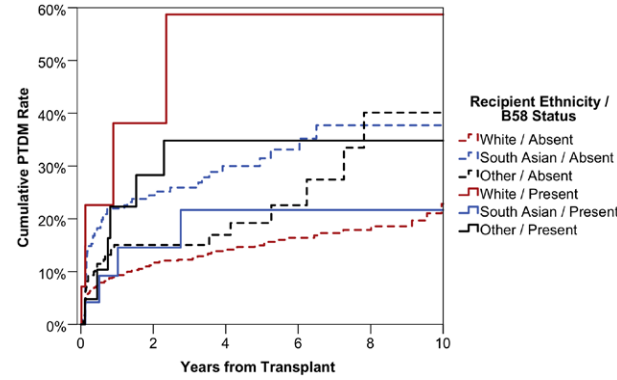

FIGURE 3. Kaplan–Meier curve of PTDM by recipient ethnicity and HLA B58 status. PTDM, posttransplantation diabetes.

(termed Indo-Asian in their study), although our observation that HLA-Cw12 is in positive linkage disequilibrium with HLA-B52 was also flagged in their analysis.[10] Similarly, Nafar et al suggest that HLA-DR8 is a predisposing factor for PTDM, but HLA-DR8 and -DQ4 exhibit strong linkage, which supports our primary association with DQ4.[20] Although the work from Reddy and colleagues[10] was conducted in a South Asian cohort, their diagnostic classification of PTDM was not aligned with international consensus guidelines,[2] and the choice of calcineurin inhibitor was mixed. This confounds findings, as the risk of PTDM is stronger for tacrolimus versus cyclosporine,[23,24] and tacrolimus remains the calcineurin inhibitor of choice as primary immunosuppressant at most transplant centers. The only other study utilizing similar immunosuppression, the work from Mazali and colleagues,[15] reported a higher frequency of HLA-DR13 in Brazilian kidney transplant recipients who developed PTDM in a retrospective analysis of 67 kidney transplant recipients. This mirrors our findings, where HLA-DR13 was observed in 20.1% of our study cohort and was significantly associated with PTDM in univariable analysis.

HLA-DQ4 is well documented for its association with the development of type 1 diabetes[25,26] and is recognized as a susceptibility gene. Our association between DQ4 and risk for PTDM is a new description among kidney transplant recipients and may reflect our analysis of a larger cohort. Howson and colleagues have shown an association between glutamic acid decarboxylase autoantibodies, islet autoantibodies that typically appear before the diagnosis of type 1 diabetes, and HLA-DQ4.[26] It could be postulated that the presence of diabetic susceptibility genes in the presence of transplant specific PTDM risk factors may underlie our observed association. However, further mechanistic work is necessary to investigate how the milieu of immunosuppression and posttransplantation pathophysiology links HLA-DQ4 and development of PTDM.

In contrast to previous publications, we performed a more comprehensive analysis of all the HLA genes from Class I and II, which may explain our novel finding of HLA-Cw12 being associated with PTDM. This is interesting, as the clinical significance of HLA-Cw12 alleles are poorly described in the medical literature and never been associated with development of diabetes. Reviewing the literature, a handful of publications report an association with HLA-Cw12 and psoriasis in Chinese[27] and Turkish[28] non-transplant populations. A review of published observational studies suggests an increased prevalence of diabetes among patients with psoriasis, but any underlying mechanistic or biological pathophysiology remains elusive.[29] Some HLA genes are associated with drug hypersensitivity (eg, HLA-B*5701 association with abacavir)[30] and could speculatively accentuate diabetogenicity of certain immunosuppressants like tacrolimus or steroids after kidney transplantation. However, this requires further investigation, and the paucity of data in this area is a major limiting factor to further our understanding of the role of HLA-Cw12 in development of clinical disease states like PTDM. Taken together, our findings reinforce recommendations from the international consensus guidelines[2] for PTDM to be considered as a distinct

pathophysiological entity in the overall classification system of diabetes mellitus.

The principal limitation of our analysis is the acknowledgment that HLA is tremendously variable in terms of individual alleles and in the distributions of combinations and haplotypes between populations. For example, whether PTDM risk is due to Cw12 or a linked drug-metabolizing gene, this could be linked to different A, B, DR, or DQ alleles in different ethnic groups and could explain why studies so far have made different observations. Therefore, our findings are important for demonstrating the importance of HLA association with risk for PTDM but also introducing the C locus into the discussion, which has previously been overlooked. The DQ4 association is interesting and appears independent from Cw12 but could hypothetically be a genetic linkage association with both linked to a "PTDM locus" or something similar.

Other limitations include being a single-center analysis, despite being the largest analysis of its type. As a retrospective study, unmeasured variables may confound the associations we have identified. Our study cohort also lacks data on some established risk factors for PTDM, such as family history of diabetes; therefore, we could not adjust for this and other potential confounders. Our analysis also focused on baseline risk variables and posttransplant factors that can contribute to PTDM (eg, rejection episodes, cytomegalovirus infection) were not incorporated. Despite having comprehensive electronic patient records to evaluate patient level data, they are susceptible to missing data, which is an inherent bias in epidemiological analyses. Correct interpretation of our results may be also affected by misclassified data and coding errors. Although we utilized contemporary diagnostic classification for PTDM, oral glucose tolerance tests were rarely performed at our center, meaning we likely underestimate the true prevalence of PTDM. In addition, some kidney transplant recipients were repatriated back to their referral hospitals (and were subsequently censored in the analysis), which may further contribute to an underestimate of the true incidence of PTDM in our baseline cohort. Our study findings may not be translatable to other populations with a different ethnic composition. Although our study cohort is representative of the local demographics of Birmingham and the broader West Midlands region of England, caution should be applied in translation of our findings nationally and internationally. Finally, our analysis is only establishing an association and should not be interpreted as implying any causality.

To conclude, our study has identified the presence of HLA-Cw12 and HLA-DQ4 in kidney transplant recipients as independent risk factors for the development of PTDM. Associations between DQ4 and development of diabetes are well described in the literature but have never been linked with PTDM, while the association between Cw12 and PTDM is completely novel, although predictable from known linkage disequilibrium with associated alleles seen in other studies. However, we believe further studies are warranted to both corroborate our observations and investigate any underlying biological mechanisms. Raising awareness of these additional risk factors, if validated in other study cohorts, can guide targeted patient counseling and improve PTDM attenuation strategies before surgery for kidney transplant candidates. However, it is likely that specific HLA alleles will vary across different patient cohorts, based upon baseline demographics, and personalized PTDM risk mitigation strategies will require obtaining insight into predominant HLA alleles within local transplant cohorts.

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