

# HLA-DQ Mismatching: Mounting Evidence for a Role in Kidney Transplant Rejection

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The HLA system consists of a group of cell surface proteins encoded for by genes located on the short arm of chromosome 6. Since the discovery of this system in the 1950s, it has become clear that HLA molecules play an important role in controlling immune responses generated by the interaction of these proteins with foreign antigens. Humans have three class 1 HLA antigens (A, B, and C) that are present on all nucleated cells and three categories of class 2 HLA antigens (DR, DQ, and DP) present only on antigen-presenting cells and lymphocytes. It is well recognized that mismatches between the HLA antigens of a recipient and donor form a major barrier to successful outcomes after kidney transplantation, increasing the risk of rejection and graft loss. Techniques for HLA typing have evolved from simple serologic methods to advanced molecular techniques (1,2) as it has become increasingly clear that serologically indistinguishable HLA molecules may have functionally distinct allelic products.

After the first International Histocompatibility Workshop in 1964, HLA matching became the cornerstone of deceased donor organ allocation policies (3,4). Although HLA mismatching remains an independent risk factor for poor allograft outcomes in the modern era (5), the quantitative contribution of HLA matching in modern allocation algorithms has decreased progressively over time. In the United States, matching of HLA-A, -B, -C, and -DR antigens was included in early allocation algorithms. With time and experience, it became evident that mismatches of class 1 HLA antigens were less detrimental to allograft outcomes than mismatches of class 2 antigens. In the current United Network For Organ Sharing point system for kidney allocation, only HLA-DR matching is included. Until recently, the effect of HLA-DQ or -DP matching or mismatching on transplant outcomes has been less certain, in part because accurate identification of these class 2 molecules has relied more heavily on DNA sequencing than the more traditionally studied HLA antigens.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Lim *et al.* (6) use data from the Australian and New Zealand Dialysis and Transplant Registry to analyze the effect of HLA-DQ mismatching on the outcomes of primary kidney transplants performed between 2004 and 2012. Of the 6107 patients receiving primary transplants during this period, 87%

were excluded from the analysis because of missing HLA-DQ molecular typing, leaving only 788 patients available for the study. Patients were classified as having either zero HLA-DQ mismatches or one or two HLA-DQ mismatches. The studied outcomes were acute rejection, graft loss, and graft function measured as eGFR. In univariate analyses, compared with patients with zero HLA-DQ mismatches, those with one or two HLA-DQ mismatches exhibited significantly higher rates of acute rejection classified as any rejection episode (16% versus 25%;  $P < 0.01$ ), late rejection ( $> 6$  months post-transplant; 2% versus 6%;  $P = 0.03$ ), or antibody-mediated acute rejection (4% versus 8%;  $P = 0.01$ ). Clinical variables included in the multivariate analyses included donor age and type (living versus deceased) and recipient age, sex, cause of ESRD, waiting time, smoking history, presence of coronary artery disease, percentage of panel-reactive antibodies, use of induction therapy, total ischemic time, and type of initial immunosuppression. There were no statistically significant associations between HLA-DQ mismatching and graft loss or graft function using either univariate or multivariate analyses.

One reason why the effects of HLA-DQ matching have been underemphasized in the past has been the assumption that HLA-DQ matching closely parallels HLA-DR matching because of linkage disequilibrium, reflecting the proximity of the two genes on chromosome 6. However, in the study by Lim *et al.* (6), concordance between HLA-DQ and HLA-DR was observed more commonly in patients who had a DQ-DR mismatch (of the 467 patients with one or two HLA-DQ mismatches, 94% also had HLA-DR mismatches) than in patients who had a zero HLA-DQ mismatch (of 321 patients with zero HLA-DQ mismatches, 54% exhibited HLA-DR mismatches). In multivariate analyses, the effect of HLA-DQ mismatching on any acute rejection episode or late acute rejection was independent of mismatching of HLA-A, -B, and -DR antigens. However, when acute antibody-mediated rejection was the dependent variable, there was a statistically significant interaction between HLA-DR mismatching and HLA-DQ mismatching, with the risk of antibody-mediated rejection observed at a higher rate only in HLA-DQ mismatched patients who also had an HLA-DR mismatch.

Results of this analysis from the large and robust Australia and New Zealand Dialysis and Transplant

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Registry help to confirm preliminary findings from other studies suggesting that HLA-DQ mismatching may influence kidney transplant outcomes. Several studies have shown that the development of *de novo* anti-DQ donor-specific antibodies (DSAs) is associated with antibody-mediated rejection, transplant glomerulopathy, and early graft loss (7–10). More recently, HLA-DQ mismatching at the epitope level has been strongly associated with the development of anti-DQ DSAs (11–13), especially in the setting of minimizing immunosuppression (13).

The study by Lim *et al.* (6) is, of course, weakened somewhat by limitations inherent in a retrospective analysis of registry data. A particular weakness is the lack of data on *de novo* DSAs that would have allowed a correlation between HLA-DQ mismatching, the emergence of *de novo* anti-DQ DSAs, and increased rates of acute rejection. Selection bias is also a concern, because the analyses were limited to patients transplanted at centers capable of performing molecular HLA typing, thus excluding a large majority of patients in the registry. Finally, despite the large size of the overall database, the numbers of patients with HLA-DQ mismatches were probably too small for the investigators to determine whether there are significant differences between one and two HLA-DQ mismatches.

Results of the study, nevertheless, confirm the importance of HLA-DQ mismatching as a predictor of acute rejection independent of multiple relevant clinical covariates and also, independent of mismatching of HLA-A, HLA-B, and possibly, HLA-DR antigens (6). Whether these results will have any effect on current allocation algorithms remains to be determined. The contribution of HLA matching to the United States allocation algorithm has been superseded by factors, such as time on dialysis, humoral sensitization, and donor clinical characteristics—all motivated to increase the utilization of deceased donor organs and increase overall longevity of transplanted kidneys (14). Thus, it seems unlikely that HLA-DQ matching will be added to the current allocation scheme, because the number of points awarded for HLA-DR matching is already small. However, the increasing recognition of either preformed or *de novo* anti-HLA-DQ DSAs and their role in acute and chronic immune injury to allografts suggest that additional research is warranted to further evaluate HLA-DQ mismatching, especially at the epitope level, as a tool for assessing the risk of acute rejection and other outcomes in kidney transplant recipients.

#### Disclosures

None.

#### References

- Dunckley H: HLA typing by SSO and SSP methods. *Methods Mol Biol* 882: 9–25, 2012
- Smith LK: HLA typing by direct DNA sequencing. *Methods Mol Biol* 882: 67–86, 2012
- Gilks WR, Bradley BA, Gore SM, Klouda PT: Substantial benefits of tissue matching in renal transplantation. *Transplantation* 43: 669–674, 1987
- Opelz G, Wujciak T, Döhler B, Scherer S, Mytilineos J: HLA compatibility and organ transplant survival. Collaborative Transplant Study. *Rev Immunogenet* 1: 334–342, 1999
- Lim WH, Chadban SJ, Clayton P, Budgeon CA, Murray K, Campbell SB, Cohnen S, Russ GR, McDonald SP: Human leukocyte antigen mismatches associated with increased risk of rejection, graft failure, and death independent of initial immunosuppression in renal transplant recipients. *Clin Transplant* 26: E428–E437, 2012
- Lim WH, Chapman JR, Coates PT, Lewis JR, Russ GR, Watson N, Holdsworth R, Wong G: HLA-DQ mismatches and rejection in kidney transplant recipients. *Clin J Am Soc Nephrol* 11: 875–883, 2016
- Willicombe M, Brookes P, Sergeant R, Santos-Nunez E, Steggar C, Galliford J, McLean A, Cook TH, Cairns T, Roufosse C, Taube D: De novo DQ donor-specific antibodies are associated with a significant risk of antibody-mediated rejection and transplant glomerulopathy. *Transplantation* 94: 172–177, 2012
- Ginevri F, Nocera A, Comoli P, Innocente A, Cioni M, Parodi A, Fontana I, Magnasco A, Nocco A, Tagliamacco A, Sementa A, Ceriolo P, Ghio L, Zecca M, Cardillo M, Garibotto G, Ghiggeri GM, Poli F: Posttransplant de novo donor-specific hla antibodies identify pediatric kidney recipients at risk for late antibody-mediated rejection. *Am J Transplant* 12: 3355–3362, 2012
- Tagliamacco A, Cioni M, Comoli P, Ramondetta M, Brambilla C, Trivelli A, Magnasco A, Biticchi R, Fontana I, Dulbecco P, Palombo D, Klersy C, Ghiggeri GM, Ginevri F, Cardillo M, Nocera A: DQ molecules are the principal stimulators of de novo donor-specific antibodies in nonsensitized pediatric recipients receiving a first kidney transplant. *Transpl Int* 27: 667–673, 2014
- Devos JM, Gaber AO, Teeter LD, Graviss EA, Patel SJ, Land GA, Moore LW, Knight RJ: Intermediate-term graft loss after renal transplantation is associated with both donor-specific antibody and acute rejection. *Transplantation* 97: 534–540, 2014
- Wiebe C, Pochinco D, Blydt-Hansen TD, Ho J, Birk PE, Karpinski M, Goldberg A, Storsley LJ, Gibson IW, Rush DN, Nickerson PW: Class II HLA epitope matching-A strategy to minimize de novo donor-specific antibody development and improve outcomes. *Am J Transplant* 13: 3114–3122, 2013
- Sapir-Pichhadze R, Tinkam K, Quach K, Logan AG, Laupacis A, John R, Beyene J, Kim SJ: HLA-DR and -DQ eplet mismatches and transplant glomerulopathy: A nested case-control study. *Am J Transplant* 15: 137–148, 2015
- Hricik DE, Formica RN, Nickerson P, Rush D, Fairchild RL, Poggio ED, Gibson IW, Wiebe C, Tinkam K, Bunnapradist S, Samaniego-Picota M, Brennan DC, Schröppel B, Gaber O, Armstrong B, Ikle D, Diop H, Bridges ND, Heeger PS: Clinical Trials in Organ Transplantation-09 Consortium: Adverse outcomes of tacrolimus withdrawal in immune-quiescent kidney transplant recipients. *J Am Soc Nephrol* 26: 3114–3122, 2015
- Israni AK, Salkowski N, Gustafson S, Snyder JJ, Friedewald JJ, Formica RN, Wang X, Shteyn E, Cherikh W, Stewart D, Samana CJ, Chung A, Hart A, Kasiske BL: New national allocation policy for deceased donor kidneys in the United States and possible effect on patient outcomes. *J Am Soc Nephrol* 25: 1842–1848, 2014

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See related article, “HLA-DQ Mismatches and Rejection in Kidney Transplant Recipients,” on pages 875–883.