The most impactful determinants of HLA-DQ de novo donor-specific antibody development and their effect on allograft survival

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Background:
HLA-DQ are the most common de novo donor-specific antibodies (dnDSA) that develop post-transplantation and correlate with rejection and allograft loss. It is unknown whether the potential for HLA-DQ molecules to form cis- or trans-heterodimers affects the risk of dnDSA development or whether certain HLA-DQ allele mismatches are more immunogenic.

Methods:
We examined a large cohort of kidney transplant recipients to comprehensively evaluate the role of HLA-DQ trans-dimerization potential and specific HLA-DQ mismatches (in particular, DQα$_1$*05 in combination with DQβ$_1$*02:01/03:01 highlighted a previous report) on the risk of dnDSA development. We also examined the impact of HLA-DQ dnDSA on post-dnDSA allograft survival relative to dnDSA against other HLA loci.

We analyzed 949 well-characterized renal transplant recipients for the relevance of cis/trans-HLA-DQ molecules, specific HLA-DQ allele mismatches, eplet mismatch, and HLA-DQ dnDSA on allograft survival. Compatible HLA-DQ trans pairs were determined based on previously published research (Figure 1).

Results:
Using maximum HLA-DQ eplet mismatch in cis- versus cis- and trans-molecules as predictors of HLA-DQ dnDSA development resulted in similar AUCs of 0.76 and 0.76, respectively. The maximum HLA-DQ eplet mismatch of the two alleles correlated with dnDSA development (HR 1.16 per mismatch, 95% CI 1.11-1.23, p<0.0001) after adjusting for the potential of the recipient (HR 1.2, p=0.6) or donor (HR 0.8, p=0.3) to form trans-HLA-DQ molecules.

In recipients with only a single HLA-DQ mismatch (n=449), no specific HLA-DQ mismatched serologic group was more likely to result in HLA-DQ dnDSA (p=0.8, Figure 2).

Figure 1. Illustrative examples of potential HLA-DQ cis and trans heterodimers

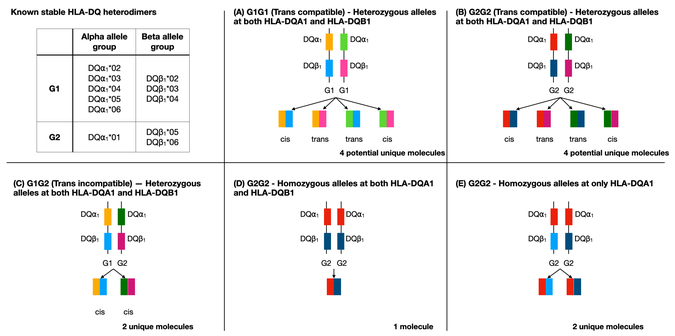


Figure 2. De novo DSA-free survival by HLA-DQ serologic mismatch groups in recipients with only a single HLA-DQ mismatch

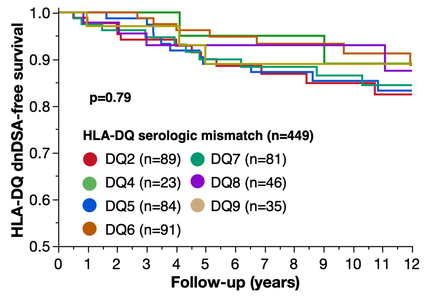


Figure 3. Maximum HLA-DQ eplet mismatch correlated with HLA-DQ dnDSA development within subgroups of HLA-DQ serologic mismatch

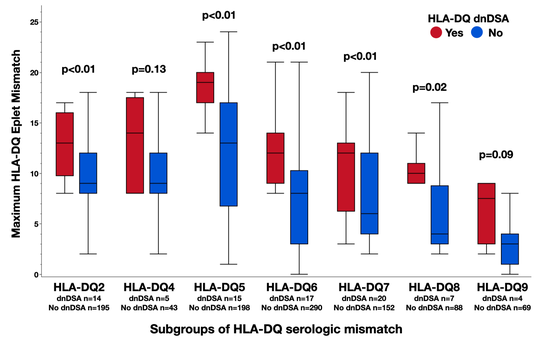


Figure 4. HLA-DQ dnDSA-free survival by HLA-DQα$_1$ and HLA-DQβ$_1$ mismatch category

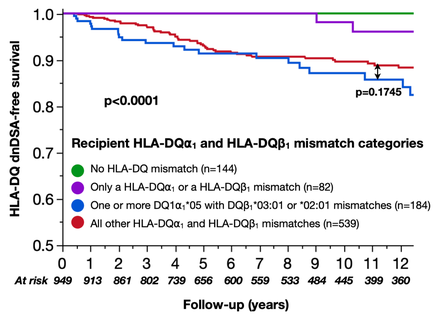
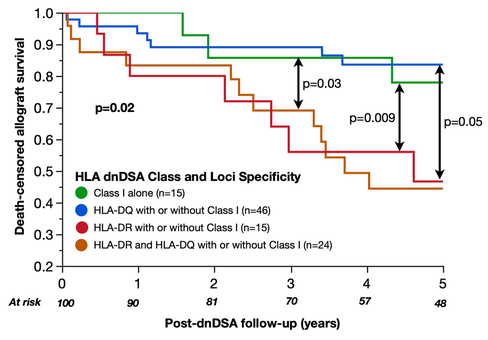


Figure 5. Death-censored allograft survival by HLA Class I and Class II dnDSA loci specificity



However, within each subgroup of serologic HLA-DQ mismatch, the maximum HLA-DQ eplet mismatch correlated with HLA-DQ dnDSA development (Figure 3).

After excluding HLA-DQα$_1$ and HLA-DQβ$_1$ mismatched molecules represented less than ten times, we found no significant difference in the frequency of dnDSA development against specific mismatched HLA-DQ molecules (n=994 molecules, p=0.3). Recipients with at least one DQα$_1$*05-DQβ$_1$*02:01/03:01 mismatch did not experience decreased HLA-DQ dnDSA-free survival compared to recipients with other HLA-DQα$_1$β$_1$ mismatches (p=0.2, Figure 4).

Compared to recipients who developed Class I dnDSA, recipients with HLA-DQ dnDSA had similar post-dnDSA death-censored allograft survival (p=0.4), while recipients with HLA-DR dnDSA (p=0.009) or both HLA-DQ and HLA-DR dnDSA had reduced (p=0.03) allograft survival (Figure 5).

Conclusions:
While specific HLA-DQ molecules were not associated with increased frequency of dnDSA development, we demonstrated that within HLA-DQ mismatched serologic groups and HLA-DQ cis/trans mismatch groups, HLA-DQ eplet mismatch predicted dnDSA development. Although HLA-DQ dnDSA development was frequent, its effect on allograft survival was less significant compared to HLA-DR dnDSA or the combination of HLA-DR and DQ dnDSA, highlighting the continuing need for HLA-DR matching in alloimmune risk assessment.

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