HLA-DQ Mismatch and Donor-Specific Antibody Formation in Lung Transplant Recipients

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Introduction

De novo donor-specific antibodies (dnDSAs) are associated with antibody-mediated rejection (AMR) in transplant recipients. Cases with 2 HLA-DQ mismatches forming 1 dnDSA (2MM1DSA) suggest unequal immunogenicity among HLA-DQ antigens, emphasizing the need to identify high-risk mismatches to optimize donor selection and post-transplant outcomes. This study examined the association between HLA-DQ mismatches, including specific HLA-DQ heterodimers, and dnDSA formation among lung transplant recipients.

Methodology

A retrospective study (2017-2024) at University Health (San Antonio, TX) analyzed 112 first time lung transplant recipients with available donor and recipient HLA-DQ typing and anti-HLA antibody testing. Patients with HLA-DQ–homozygous donors or lacking anti-HLA reagent coverage were excluded. HLA-DQ allele typing, mismatch count, heterodimer combinations, and dnDSA presence were extracted from the electronic medical record and analyzed.

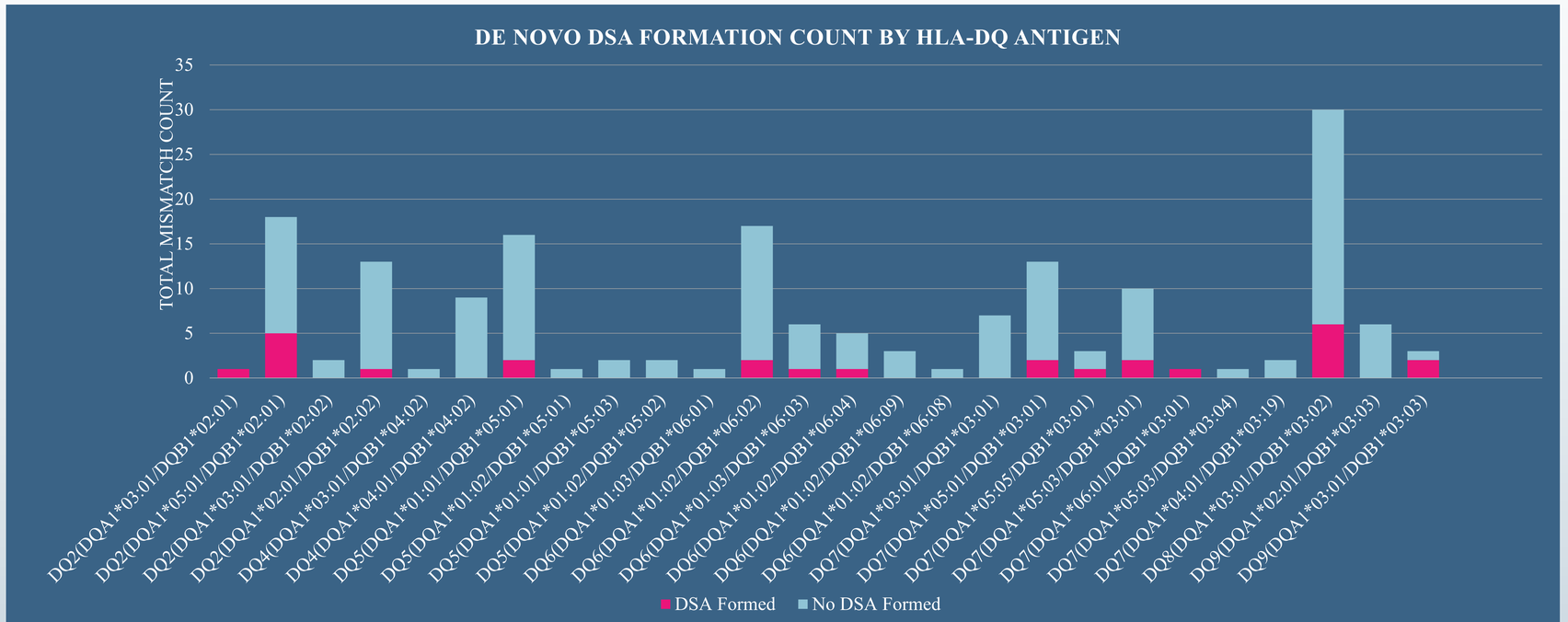


Figure 1. De Novo DSA Formation Count by HLA-DQ Mismatch Antigens.
Frequency of each HLA-DQ mismatch (n=174) between transplanted lung patient (n=106) and the development of HLA-DQ dnDSA.

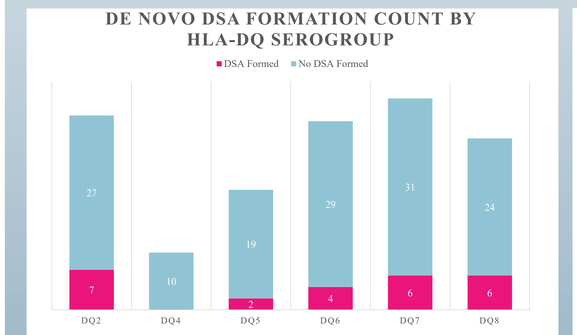
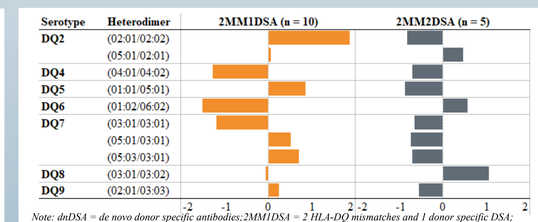


Figure 2. De Novo DSA Formation Count by HLA-DQ Mismatch Serogroup. Frequency of each HLA-DQ mismatch (n=174) between transplanted lung patient (n=106) and the development of HLA-DQ dnDSA.



Note: dnDSA = de novo donor specific antibodies;2MM1DSA = 2 HLA-DQ mismatches and 1 donor specific DSA; 2MM2DSA = 2 HLA-DQ mismatches and 2 donor specific DSA

Figure 3. Adjusted Standardized Residuals of Donor Heterodimers Stratified by Mismatch to dnDSA Ratio.
Adjusted standardized residuals of case counts > 5 did not identify any cells with significant deviation (|z| > 1.96), suggesting no specific serotype–DSA combination disproportionately contributed to the overall association. However, DQ2(DQA1*02:01/DQB1*02:02) showed increased development of dnDSA than statistically expected (z = 1.88).

Table 1. Frequencies of Patient HLA-DQ Mismatch Counts versus HLA-DQ dnDSA Counts

HLA-DQ Mismatch Count	HLA-DQ dnDSA Count 0	1	2
0	6	N/A	N/A
1	32	7	N/A
2	52	10	5

Note: dnDSA = de novo donor specific antibodies;
n = 112 lung transplant recipients

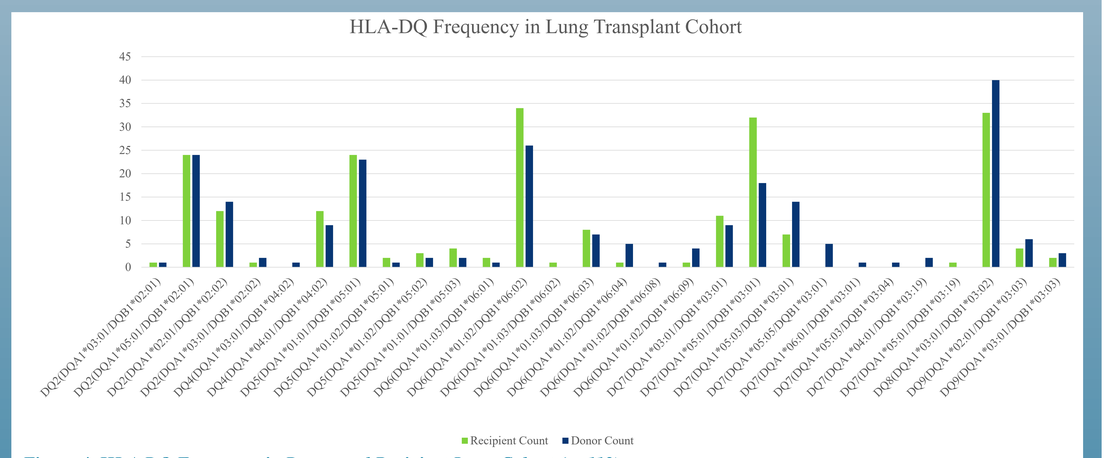


Figure 4. HLA-DQ Frequency in Donor and Recipient Lung Cohort (n=112)

Results

Frequency table for HLA-DQ mismatch and HLA-DQ dnDSA showed 22 patients developed HLA-DQ dnDSA (Table 1) with most patients making anti-HLA-DQ2 antibodies (Figure 1; Figure 2). Chi-Square Test and Fisher's Exact Tests (Jamovi v2.7.9) evaluated independence between HLA-DQ mismatch count and dnDSA formation with no significant correlation observed. A significant difference was observed for donor heterodimer (p=0.035) and donor HLA-DQA1 subunits (p=0.035); however, post-hoc sub-analysis to obtain adjusted standardized residuals (ASR) for pattern identification revealed no statistical significance (Figure 3). While trends were observed, there were no statistically significant donor HLA-DQ mismatches that presented a greater risk of immune sensitization.

Conclusion

Although an upward trend in HLA-DQ dnDSA formation was observed with increasing HLA-DQ mismatches, it did not reach statistical significance. In the case of 2MM1DSA, ASR analysis revealed HLA DQ2(DQA1*02:01/DQB1*02:02) was the most common antibody formed in this group. However, only 9% of the cohort were 2MM1DSA limiting the feasibility of the intended investigation. The absence of a detectable pattern in cases with dual mismatches forming a single dnDSA suggests that immunogenicity among HLA-DQ loci may vary in ways not captured by mismatch count alone. These findings highlight the need for a larger prospective study to determine trends in development of dnDSA in patients with HLA-DQ mismatches and to correlate findings with chronic lung allograft dysfunction (CLAD).

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References