# A retrospective analysis to evaluate if HLA-DPB1 expression level and T cell epitope disparity between kidney donors and recipients can influence the development of de novo HLA-DPB1 donor specific antibodies

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## Introduction:

De novo donor specific antibodies (dnDSA) can develop following kidney transplantation as a result of allorecognition of mismatched HLA. This can lead to antibody mediated rejection, a significant cause of graft failure. To avoid this, HLA matching is essential to kidney allocation. However, the clinical significance of mismatching at certain HLA loci, including HLA-DPB1 remains unclear. In Haematopoietic stem cell transplantation (HSCT), it has been shown that, along with HLA-DPB1 allele mismatch, HLA-DPB1 expression level and T cell epitope (TCE) disparity can also influence transplantation outcome. (1-4) Retrospective studies have demonstrated that certain HLA-DPB1 mismatches are associated with a lower risk of post-transplant complications. (1-5) Using this information, in silico models have been developed that allow for prospective consideration of HLA-DPB1 mismatches prior to HSCT, providing a prediction of how the mismatch will affect the outcome of a transplant. (2,5) The two models work by categorising mismatched HLA-DPB1 alleles either by their expression level or TCE group. (2,5) It is not known whether differences in HLA-DPB1 expression level, and TCE group increase the risk of a recipient developing HLA-DPB1 dnDSA following a kidney transplant. Studies have considered the effect of expression on the development of HLA-DPB1 dnDSA; however, they arrive at conflicting findings. (6-8) Here we investigate if these factors influence the development of HLA-DPB1 dnDSA following kidney transplantation.

## Methods:

- In 131 HLA-DPB1 mismatched kidney transplant donor-recipient pairs, we retrospectively applied the in-silico models utilised in HSCT to determine the predicted risk associated with HLA-DPB1 mismatches.
- All patients had pre- and post-transplant HLA antibody results from single antigen bead testing available, performed using the LABScreen Single Antigen kit (One Lambda, Canoga Park, CA).
- All donors had HLA-DPB1 typing available to determine the presence of HLA-DPB1 dnDSA.
- Patients without HLA-DPB1 typing were typed using Next Generation Sequencing using the ALLType™ NGS typing kit (One Lambda, Canoga Park, CA) on the Illumina Miseq platform and analysed using TypeStream™ Visual NGS analysis software.
- Using the HLA-DPB1 typing information of each patient and donor, the NMDP Expression of DP antigens tool (ExPAT) and IPD-IMGT/ HLA DPB1 T-Cell Epitope Algorithm v2.0 were used to determine if the HLA-DPB1 mismatch was expression favourable/ unfavourable or permissive/ non-permissive, respectively.

## Results:

- **HLA-DPB1 expression level significantly influences the development of HLA-DPB1 dnDSA (P=0.0045).**

HLA-DPB1 expression level is dictated by the rs9277534 A/G single nucleotide polymorphism. High expression is linked with rs9277534-G and low expression is linked with rs9277534-A. (2) Recipients who developed HLA-DPB1 dnDSA (HLA-DPB1 dnDSA+) and those who did not (HLA-DPB1 dnDSA-) were divided into two groups, a high-risk expression combination GX:AA (Donor: Recipient) (X=A or G) and all other non-GX:AA expression combinations. Our results show HLA-DPB1 expression level significantly influences the development of HLA-DPB1 dnDSA. (P=0.0045).

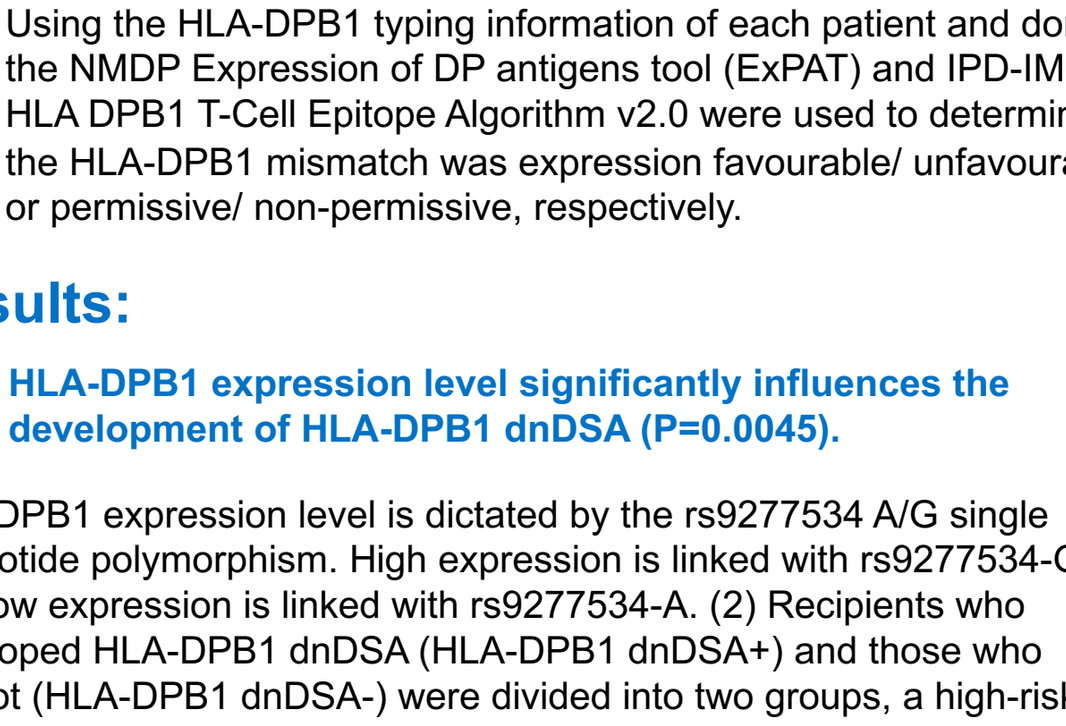


**Figure 1:** HLA-DPB1 expression level significantly influences the development of HLA-DPB1 dnDSA in patients with a low expression HLA-DPB1 genotype.

- **HLA-DPB1 expression level significantly influences the MFI level of HLA-DPB1 dnDSA (P=0.0113)**

Recipients with a high-risk expression mismatch were shown to develop HLA-DPB1 dnDSA with a significantly higher mean fluorescence intensity (MFI) when compared to recipients receiving a graft from a low expressor donor. (P=0.0113).

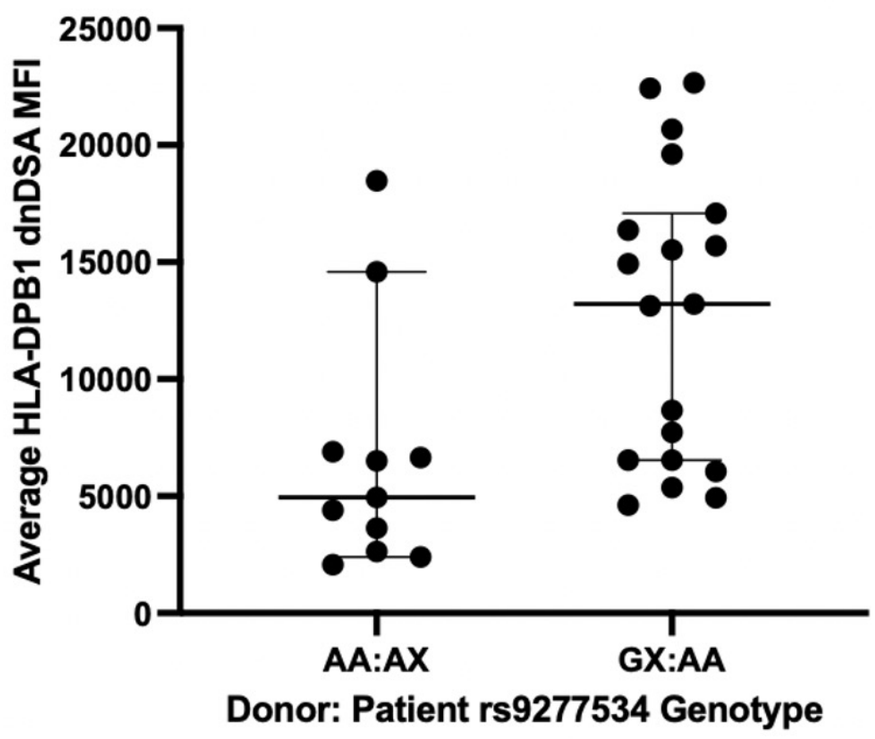


**Figure 2:** HLA-DPB1 donor expression level significantly influences HLA-DPB1 antibody production.

- **HLA-DPB1 TCE mismatch does not influence the development of HLA-DPB1 dnDSA (P=0.2124)**

HLA-DPB1 mismatches were categorised as either permissive, non-permissive graft versus host (GvH) or non-permissive host versus graft (HvG). The high-risk combination for kidney transplantation was determined to be a non-permissive (HvG) HLA-DPB1 mismatch. Our results show TCE mismatch did not influence the development of HLA-DPB1 dnDSA (p=0.2124).

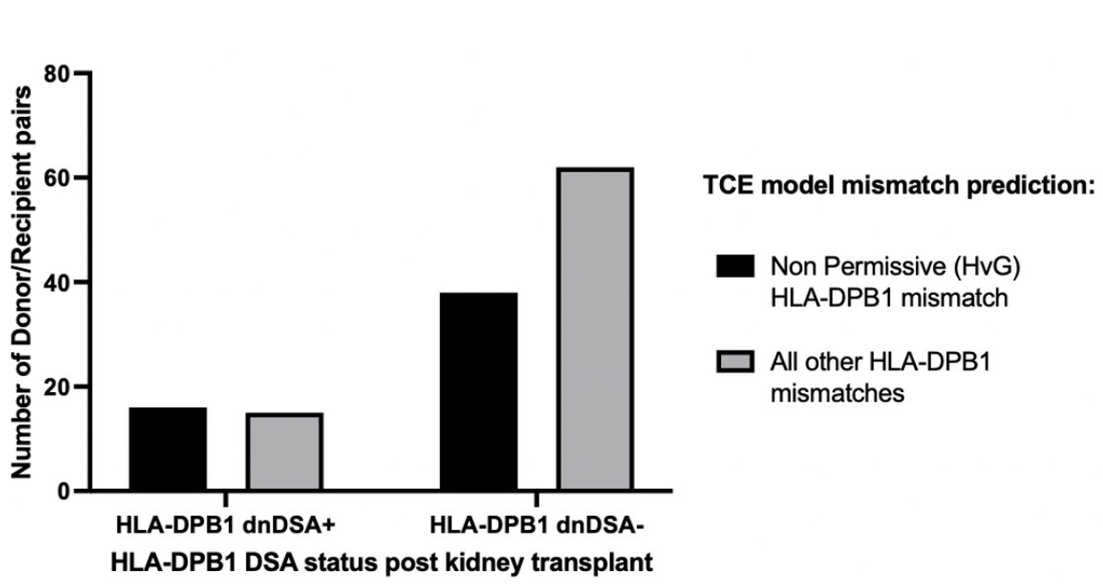


**Figure 3:** HLA-DPB1 TCE disparity between kidney recipients and donors does not influence the development of HLA-DPB1 dnDSA.

## Conclusion:

Here we describe a significant influence of HLA-DPB1 expression level, but not TCE group, on the development of HLA-DPB1 dnDSA following kidney transplantation. We propose low expression recipients are more likely to recognise HLA-DPB1 antigens on a high expressor donor kidney and are therefore more likely to develop HLA-DPB1 dnDSA. Furthermore, we propose the immune response against high expression HLA-DPB1 alleles to be stronger, resulting in HLA-DPB1 dnDSA with higher MFIs. Further studies with a larger cohort are required to confirm these findings.

## References:

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