Population Analysis of HLA Eplet and Allele Frequencies to Assess the Feasibility of Eplet-Matching in Canada

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INTRODUCTION

- Antibody-mediated rejection (AMR) is a leading cause of long-term kidney transplant failures [1]
- Kidney patients and donors matched at their histocompatibility human leukocyte antigen (HLA) genes are associated with lower AMR risk[2]
- There are >20,000 HLA alleles, making it difficult to match[2]
- Antibodies recognize and bind to eplets, clusters of amino acids on HLA[2]
- "Eplet-matching" is a more precise and biologically-relevant matching tool
- There are far fewer eplets than alleles: potentially making eplet-matching feasible in Canada[3]

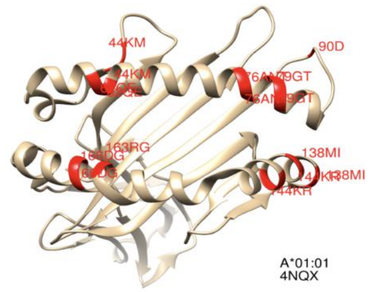
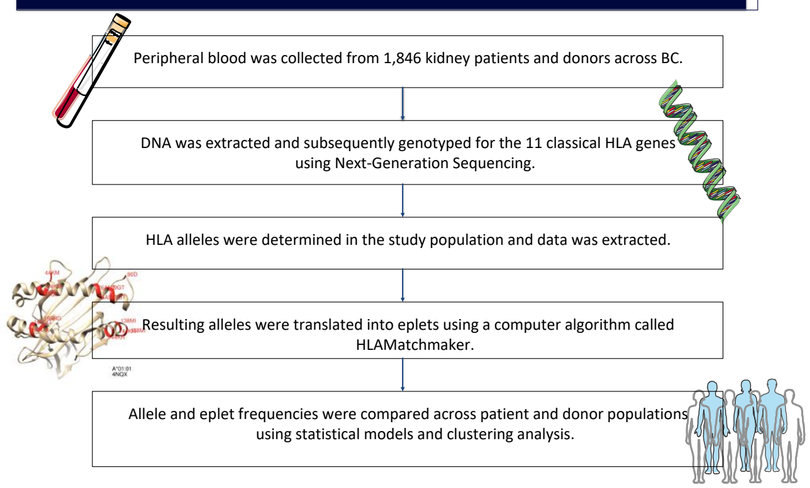


Fig 1. Ribbon diagram of the top-down view of HLA protein A*01:01. Eplets are highlighted in red.

AIM

This study describes HLA allele and eplet frequencies in kidney patient and donor populations in BC to compare the likelihood of matching by each method.

MATERIALS AND METHODS

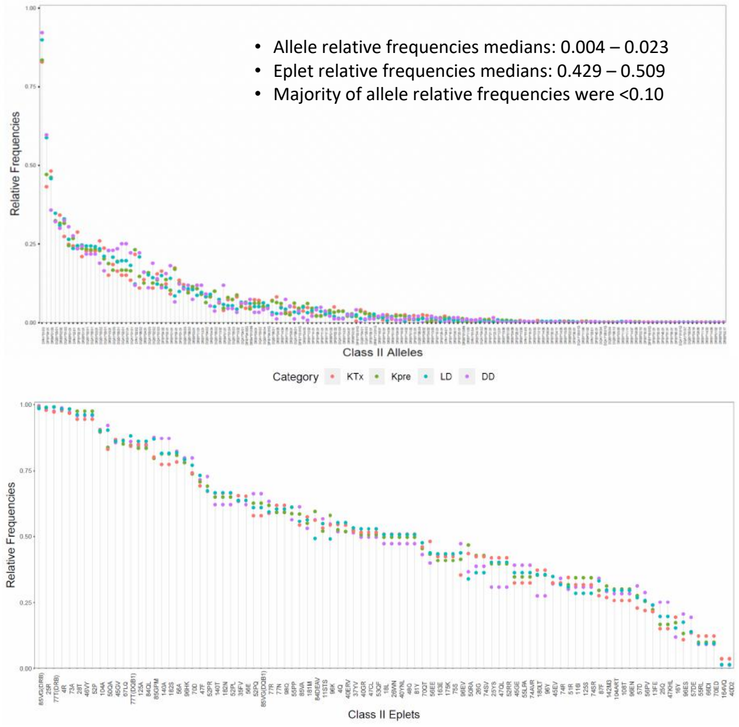


RESULTS

1,846 patients and donors were included in the study population

- 438 transplanted patients (KTx)
- 611 pre-transplant patients (KPre)
- 554 potential living donors (LD)
- 243 deceased donors (DD)

Allele relative frequencies occur at lower values than eplets



The translation of alleles into eplets results in 59% reduction in HLA complexity with a bidirectional relationship between alleles and eplets

- The 361 alleles identified in the study population translated into 150 eplets
- Multiple eplets are encoded by many alleles (e.g. 69TNT)
- Some eplets were encoded by at 2 alleles (163RG), where some by 90 alleles (131S)

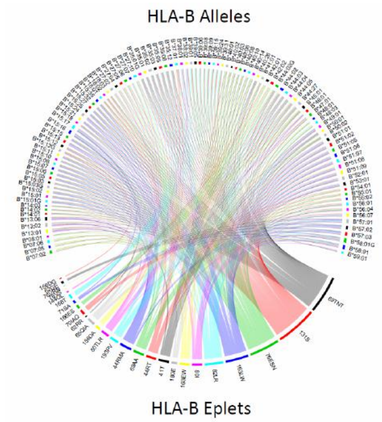


Fig 3. Chord diagram depicting the bidirectional relationship between all HLA-B alleles (n=107) identified in the study population and all the eplets (n=26) coded by them.[4]

RESULTS

Clusters of subjects were grouped into three distinct eplet patterns, the HLA epitype

- Using k-means clustering, three clusters were identified in the total study sample for both class I and class II
- Each cluster represents a pattern of eplets predominant in individuals in their relevant cluster

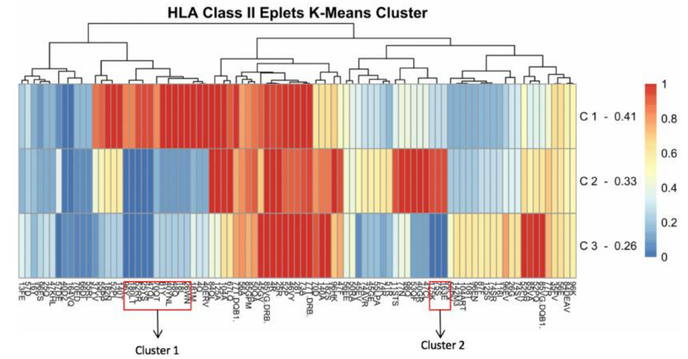


Fig 4. Cluster analysis for class II HLA eplets in the total study population. Eplets that are predominant in their respective cluster are boxed in red. Frequent eplets are coloured red, while rare eplets are blue.

Subjects segregate into different epitype clusters with distinct frequencies

- The relative frequency of each cluster in the patient and donor groups were determined
- Clusters are dependent on the patient/donor group for HLA class I (p-value < 0.001) but independent for class II (p-value = 0.237).
- Cluster 1 of class I is smaller in the transplant (KPre, KTx) than in the donor (DD, LD) cohorts. The eplets 76ANT, 44KM3, 163RG, unique to cluster 1, are mostly contributed by alleles A*01:01, A*01:02.

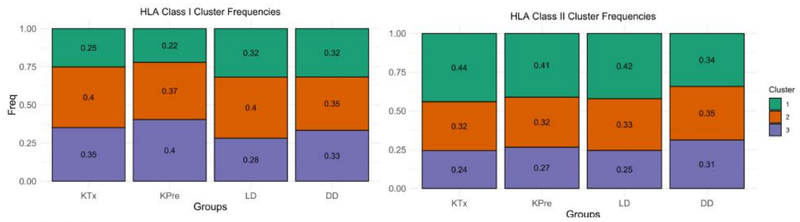


Fig 5. The frequency of clusters for class I (left) and class II (right) in the patient and donor groups.

CONCLUSION

- Conversion of alleles to eplets result in a significant reduction in HLA complexity
- Kidney patient and donor populations share common eplets with similar eplet frequencies
- HLA epitype frequencies vary between the cohorts for class I but not for class II
- Overall, the results support the use of eplets in histocompatibility matching for improving long-term transplant outcomes

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