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HLA Eplet Frequencies Reduce Genetic Complexity and Provide a Foundation for a National Eplet-Matching Program

Learning Objectives

1. To define the role of HLA eplet-matching in kidney transplantation

2. To describe HLA allele and eplet frequencies in kidney patient and donor populations in BC

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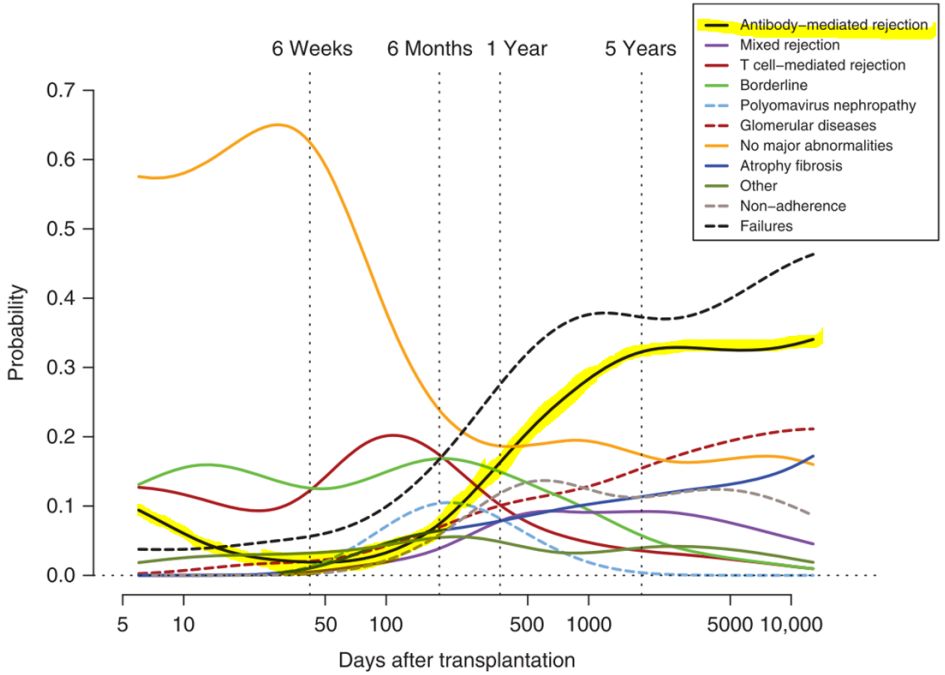
Kidney Transplantation and Antibody-Mediated Rejection (AMR)



Tonelli M. *et al. Am. J. Transplant.* **11** 2093–2109 (2011).
Sellarés J. *et al. Am. J. Transplant.* **12** 388–399 (2012).

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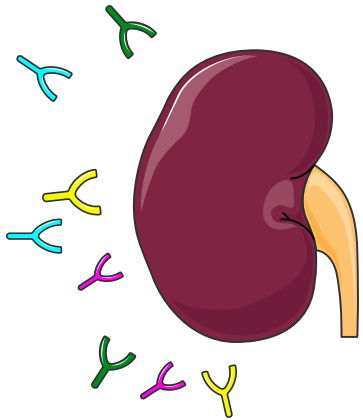
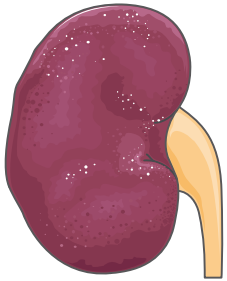
AMR

- The recipient's immune system makes antibodies targeted against foreign proteins expressed on the donated kidney



- Complement pathway
- Inflammatory response
- Activation of macrophages and NK cells



Graft rejection

- These proteins are the **human leukocyte antigens (HLA)**

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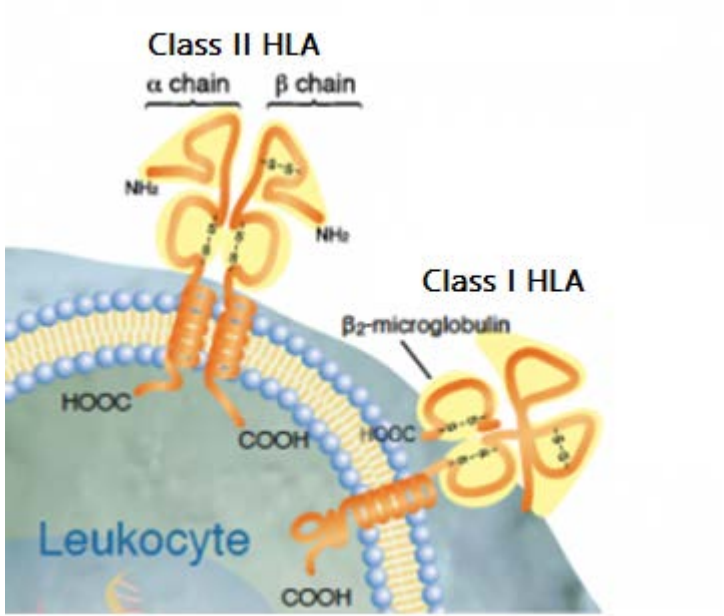
Human Leukocyte Antigens (HLA)

- Essential for the adaptive immune system to respond to foreign molecules
- 11 clinically relevant HLA genes on chromosome 6:
  - A
  - B
  - C

  Class I
  - DRB1
  - DRB3
  - DRB4
  - DRB5
  - DQB1
  - DQA1
  - DPA1
  - DPB1

  Class II



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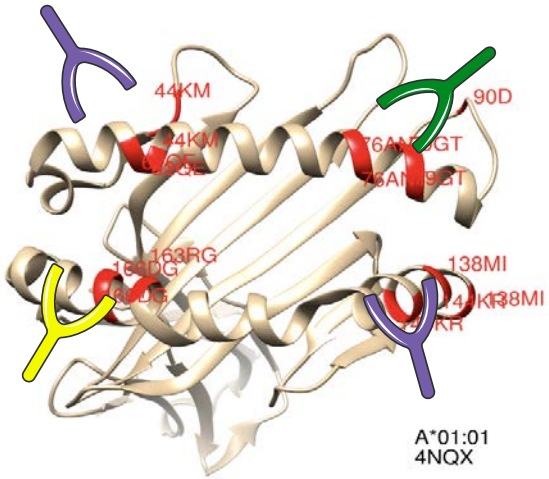
HLA Eplets

- Antibodies bind to sections of amino acids on the surface of the protein
- **Eplets** are clusters of 2 - 5 polymorphic amino acids that are essential to antibody binding



Top-down view of an HLA molecule with eplets highlighted in red

Duquesnoy, R. J. *Transpl. Immunol.* **31**, 1–6 (2014).

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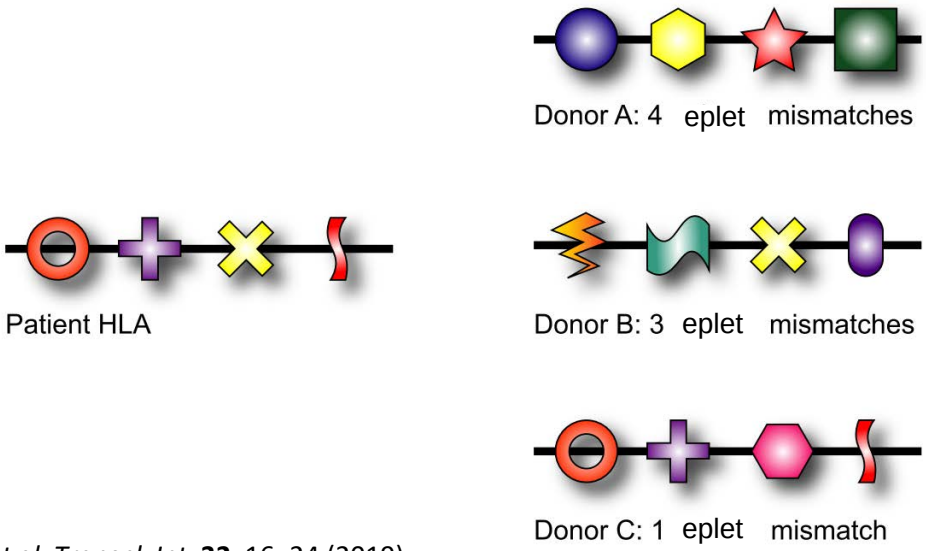
HLA Eplet-matching

- **Eplet-matching**: matching patients and donors by their HLA eplets
- The recipient's immune system will not mount a response against eplets shared between the recipient and donor



Modified from Kramer, C. S. M. *et al. Transpl. Int.* **32**, 16–24 (2019).

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Eplet-Matching in Kidney Transplantation

- Multiple studies have shown matching by eplets result in decreased risk of de novo donor-specific antibodies, transplant glomerulopathy, rejection, and graft loss
- Importantly, there are far fewer documented HLA eplets than alleles

Nevins, T. E. et al. *J. Am. Soc. Nephrol. 28, 3353–3362 (2017).*
Wiebe, C. et al. *Am. J. Transplant. 13, 3114–3122 (2013).*
Wiebe, C. *et al. Am. J. Transplant*. 19, 1708–1719 (2019).
Sapir-Pichhadze, R. *et al. Am. J. Transplant*. (2015).

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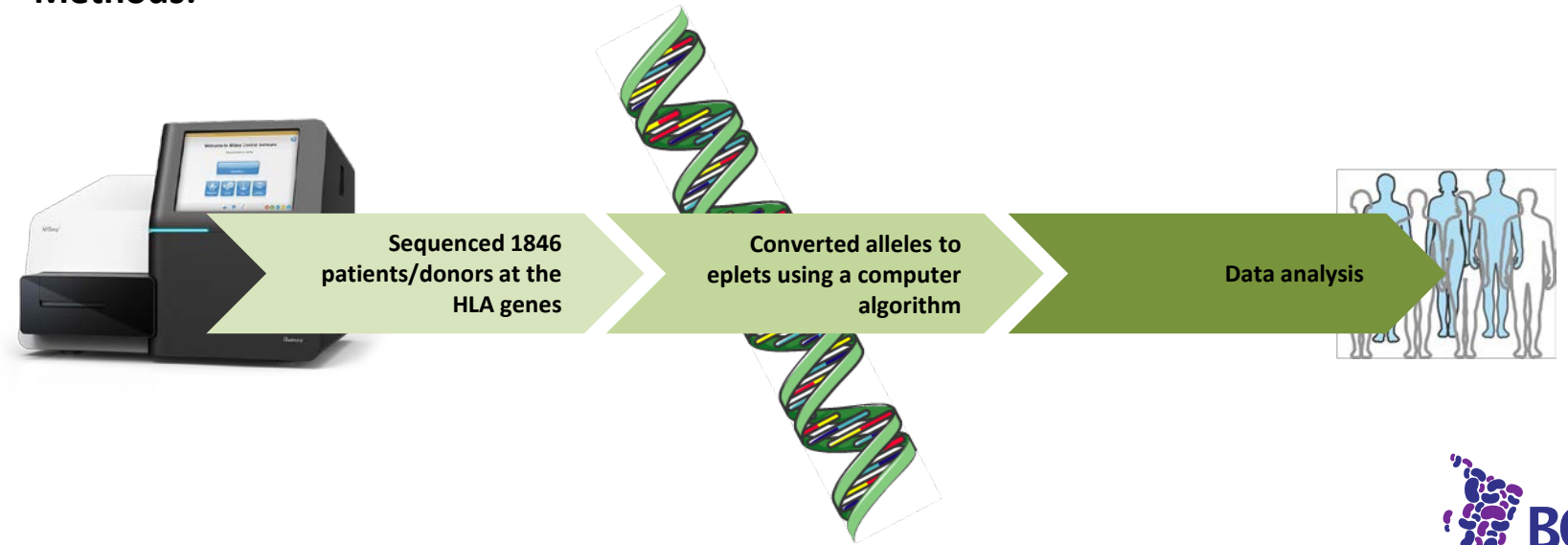
Research Design

Aim: To describe HLA allele and eplet frequencies in kidney patient and donor groups in BC and compare the likelihood of matching by each method.

Methods:



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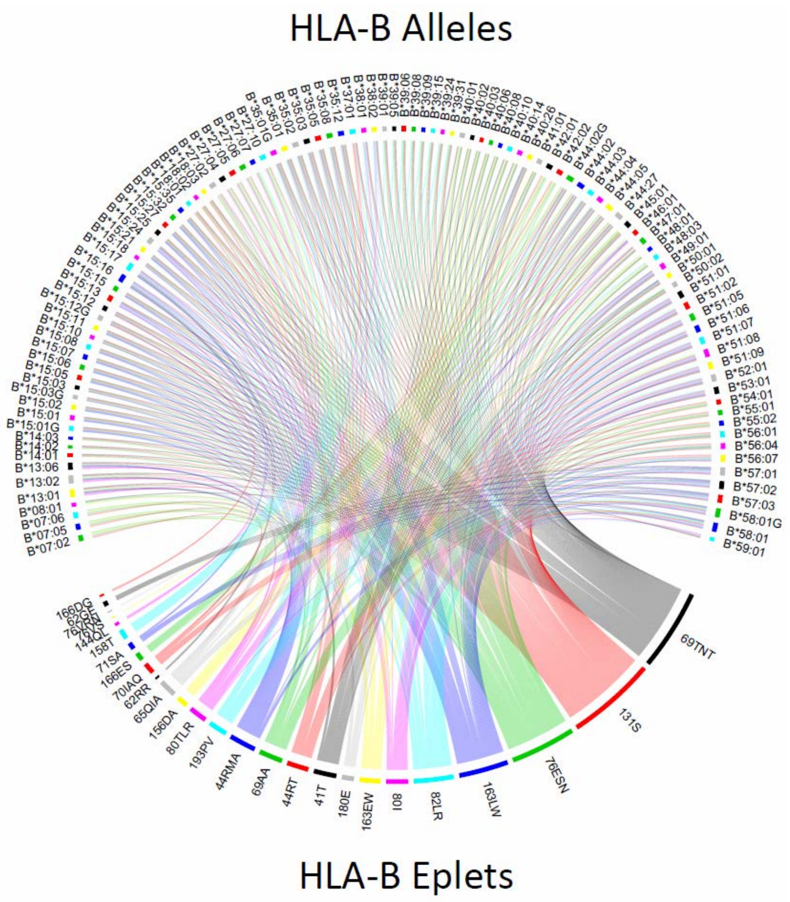
Conversion from Alleles to Eplets Reduce HLA Complexity



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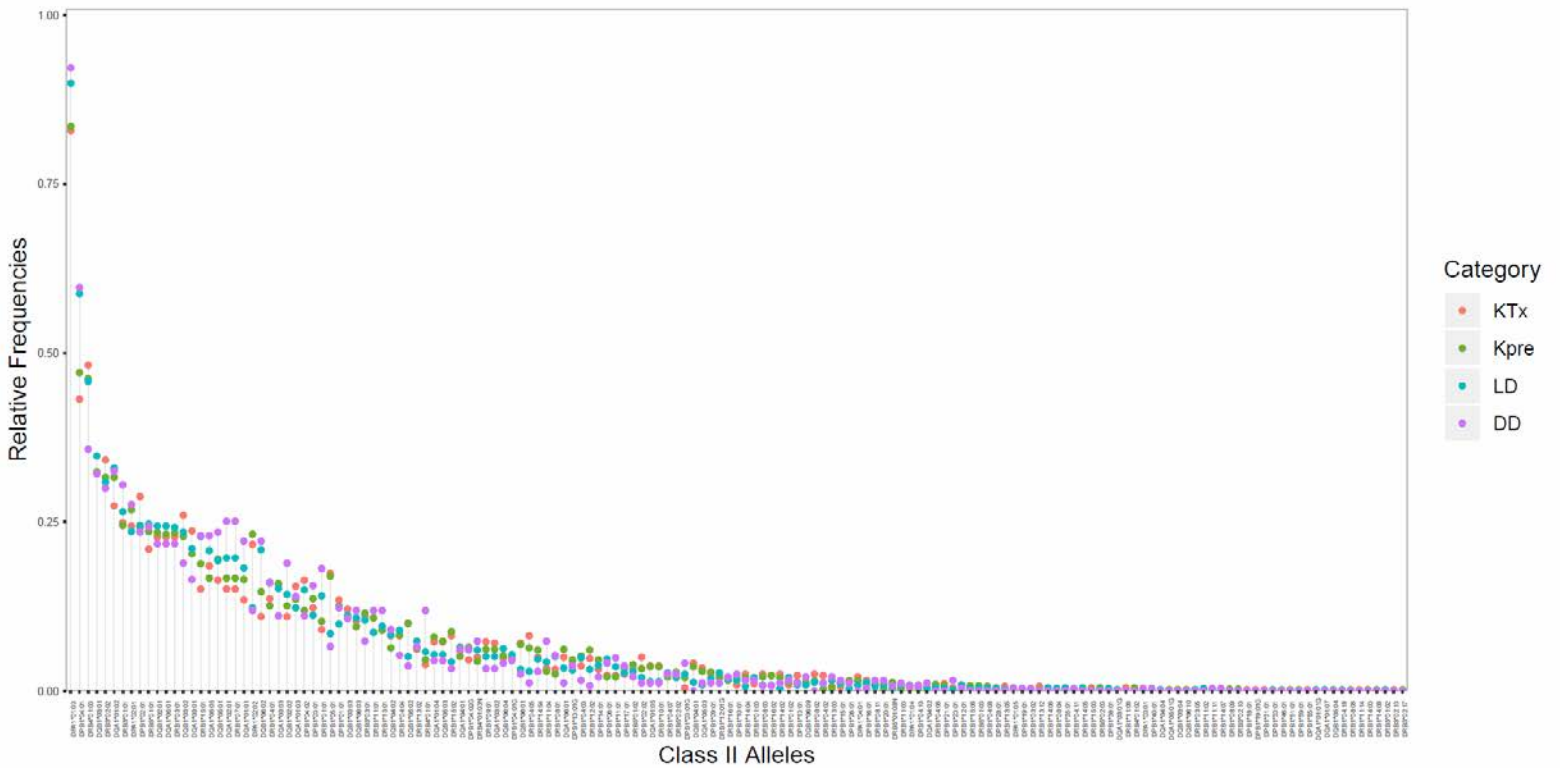
Conversion from Alleles to Eplets Reduce HLA Complexity

- 361 alleles converted into 150 eplets, resulting in a 59% reduction in genetic complexity
- Class I alleles encoded 0 – 11 eplets
- Class II alleles encoded 0 – 17 eplets

HLA Allele Frequencies



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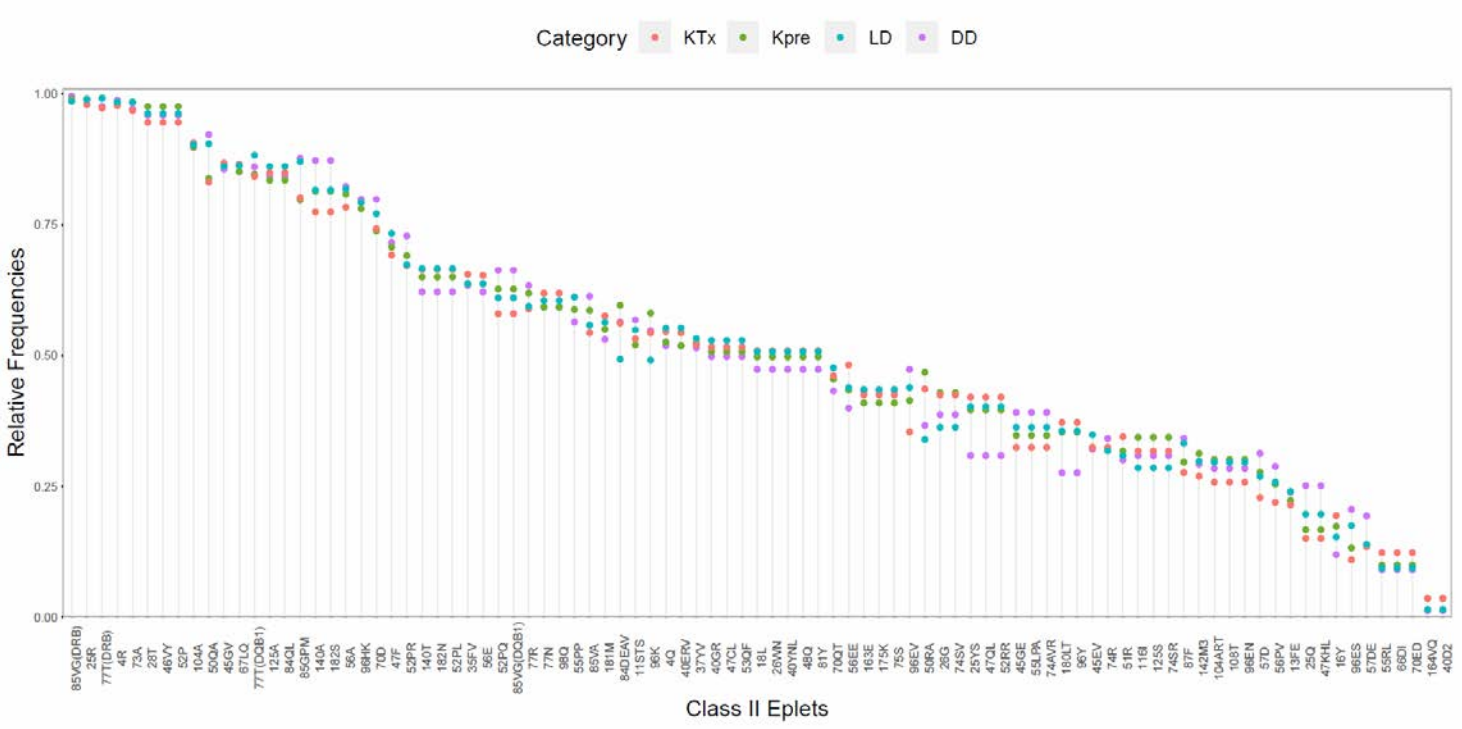
HLA Eplet Frequencies



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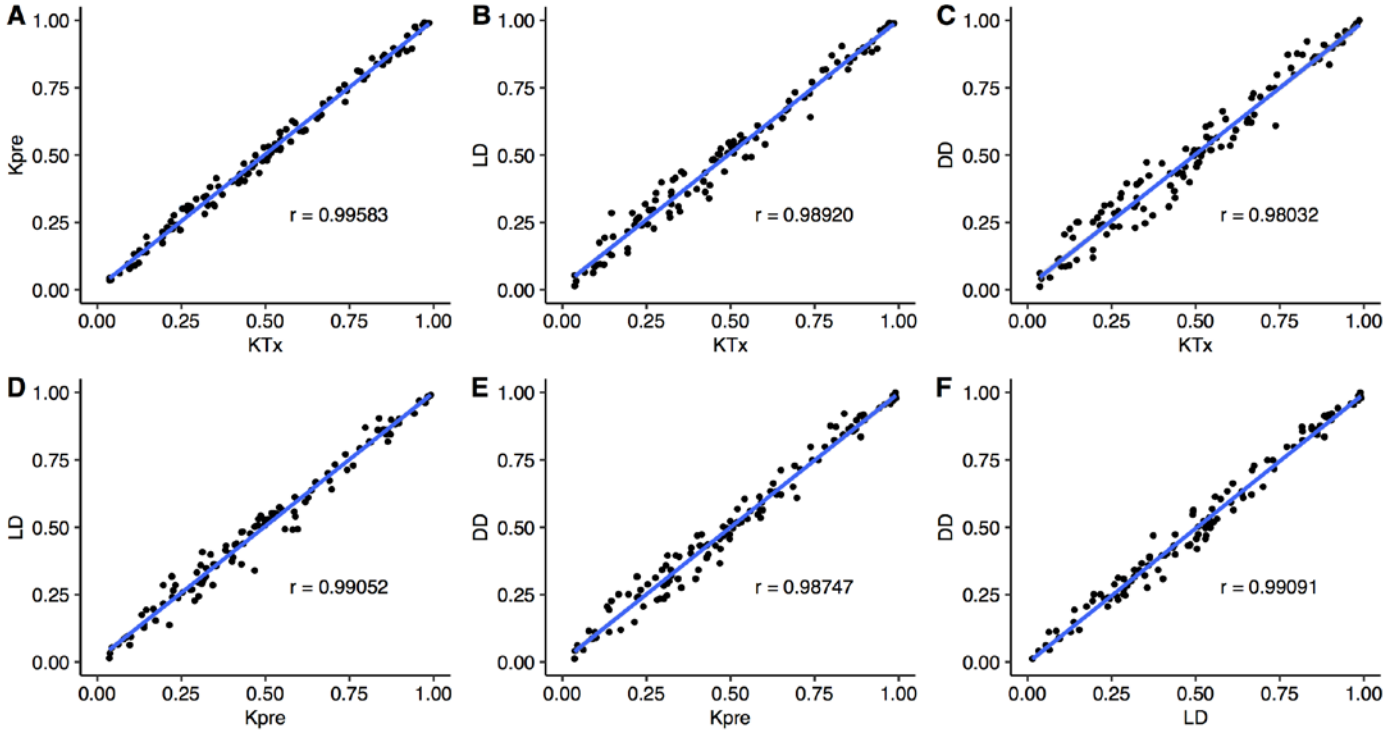
Eplet Frequencies Compared Between Patient and Donor Groups



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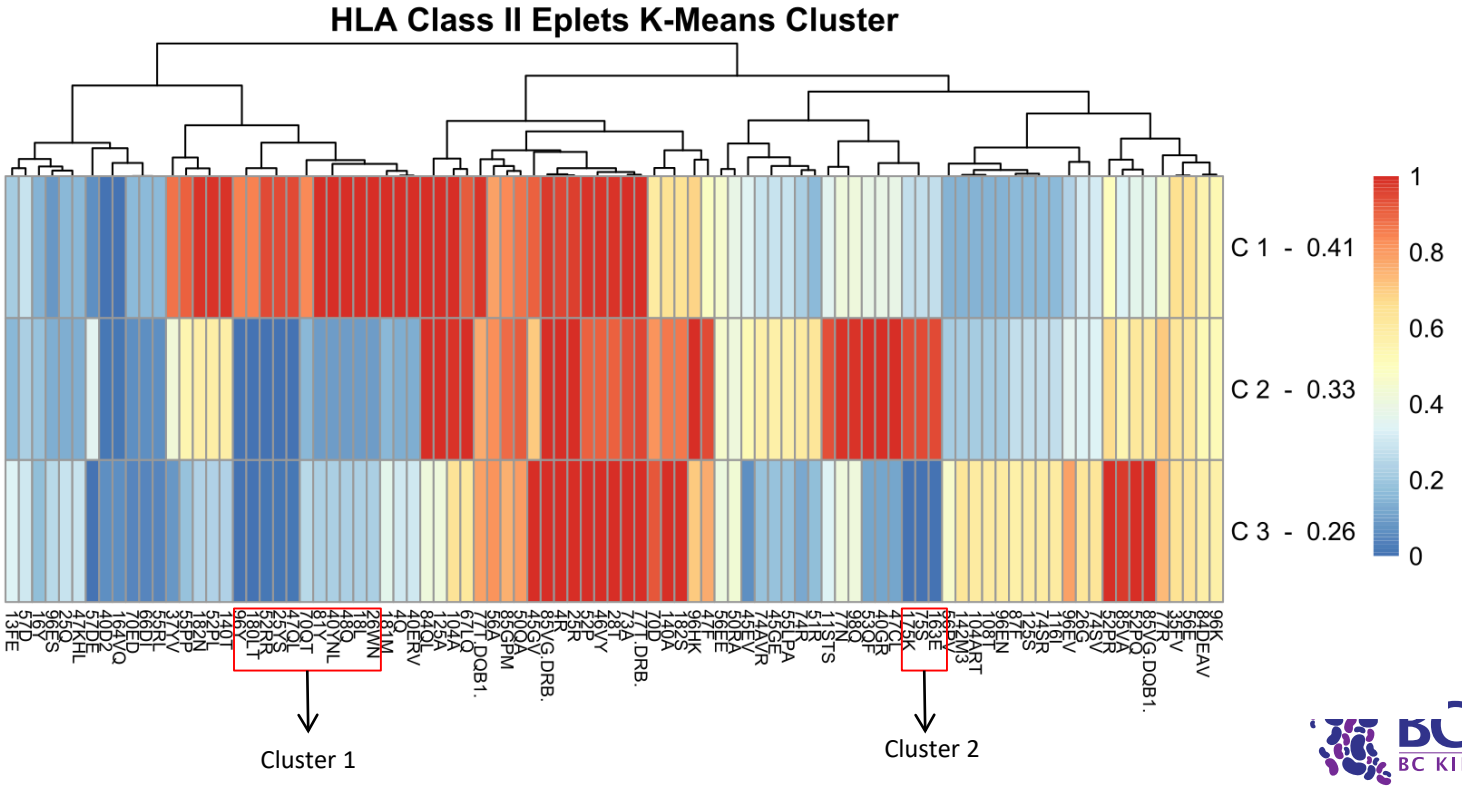
Clustering Patients and Donors by their Eplet Expression Patterns (Epitypes)



Conclusions

- Eplets reduce the HLA complexity in a BC study sample
- Patients and donors show similar eplet frequencies
- The study sample grouped into 3 clusters expressing similar eplet profiles, called epitypes
- Overall, the results support the feasibility of eplet-matching in BC in efforts to improve long term transplant outcomes

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- Dr. Rene Duquesnoy
- Dr. Frans Claas

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