Immunological assessment of Aboriginal Australian transplant recipients

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National Transplantation Service Australian Red Cross Blood Transfusion Service

Darwin October 2013

Centre for Clinical and Experimental Transplantation

Aboriginal Australian Migration

Migration to Australia 45-50,000 years ago

Approximately 2000 generations

Nomadic tribal life

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Immunologic Assessment

- Blood group
- General Immune characteristics
- KIR receptors
- HLA
- Eplet matching
- Allocation

Blood group distribution

TABLE 1

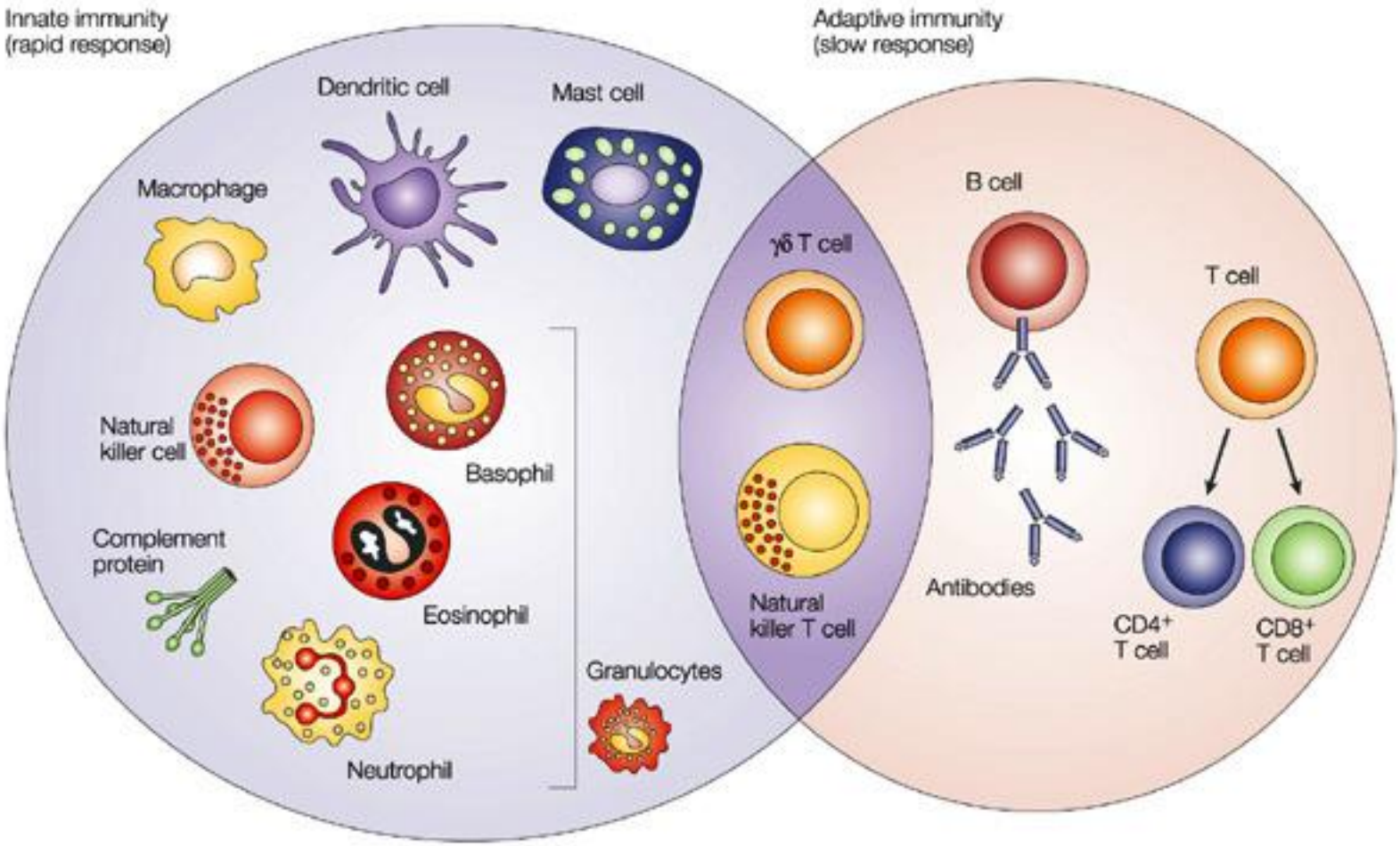
A-B-O blood groups in Northern Territory and South Australian aborigines

LOCATION AND DATE	NUMBER TESTED	BLOOD GROUPS		
		O	A_1	B
Darwin N.T. 13. 3.51; 5. 2.52.	30	23	6	1
Elsey Station, N.T. 5. 5.49.	12	9	3	0
Yuendumu, N.T. 3. 9.51.	93	44 47%	49 53%	0
Ernabella, S.A. 28. 4.50.	32	16	16	0
Totals	167	92 55.1%	74 44.3%	1 .6%

R. T. SIMMONS,[1] J. J. GRAYDON[2] AND N. M. SEMPLE[3]

Commonwealth Serum Laboratories, Melbourne, Australia

Innate and Adaptive Immunity in Transplantation



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Innate Immunity in Aboriginal Australians

- WCC normal
- Eosinophillia related to parasite infection
- Complement pathways – increased C4 null alleles
- Mannose-binding lectin – restricted polymorphisms
- Natural Killer Cells – number increased

Adaptive Immunity

- Lymphocyte count slightly lower than Caucasians
- Lower CD4+ T cells reduced response to PHA, ConA, PWM
- Immunoglobulin levels generally higher

Adaptive Immunity

Table 3 Immunoglobulin levels in Australian Aborigines

	IgG[1]	IgA[1]	IgM[1]	IgE[2]
Australian Aborigines (Adults n = 104)	25.1 ± 1.0[1]	4.9 ± 0.26[1]	1.6 ± 0.09[1]	49,900 ± 7,400[2]
Australian Aborigines (Children n = 60)	18.9 ± 0.72	1.8 ± 0.14	1.5 ± 0.09	
Laboratory normal (adults, range)	6.5 - 16	0.6 – 4.0	0.5 – 3.0	< 150

[1]Mean ± SE (g/l)

[2]Mean ± SE (IU/l)

Roberts-Thomson et al Asia Pac J Aller Immun 2005

Lower rate of HLA related immune diseases in Aboriginal Australians

Table 1 Immune disorders in Australian Aborigines

High frequency	Low or rare frequency
Rheumatic fever	Lymphoma/myeloma
SLE/DLE	Atopic disorders
Infections	Thyroid disease
Post-streptococcal glomerulonephritis	Polymyositis
	Vitiligo
	Multiple sclerosis
	Rheumatoid arthritis
	Biliary cirrhosis
	CREST
	Coeliac disease
	Juvenile onset diabetes
	Pernicious anaemia
	B27 related arthropathies
	Psoriasis

Roberts-Thomson et al Asia Pac J Aller Immun 2005

Auto-immune serological findings Aboriginal Australians

Table 2 Serological findings in Australian Aborigines

High frequency	Low or rare frequency
ANA	MPO
Ro/La	PR3
RNP	Centromere
DNA	Endomysial
Cardiolipin	Mitochondrial
RF	
↑ Ig's	
↑ CRP	

Roberts-Thomson et al Asia Pac J Aller Immun 2005

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Sensitization in ATSI

- 357 patients from SA/NT
  - 117 class I current antibody +ve
  - 17 class I current antibody >80%
  - 49 class II antibodies
  - Mixture of cell-based and solid phase assays therefore under estimates degree of sensitization

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Previous Infections

- HTLV
- Otitis Media
- Scabies
- S.pneumoniae

HTLV-I & II infection

- HTLV-I in 14% Indigenous (<1% blood donors)

  Bastian I, MJA 1993; 159 (1): 12-6

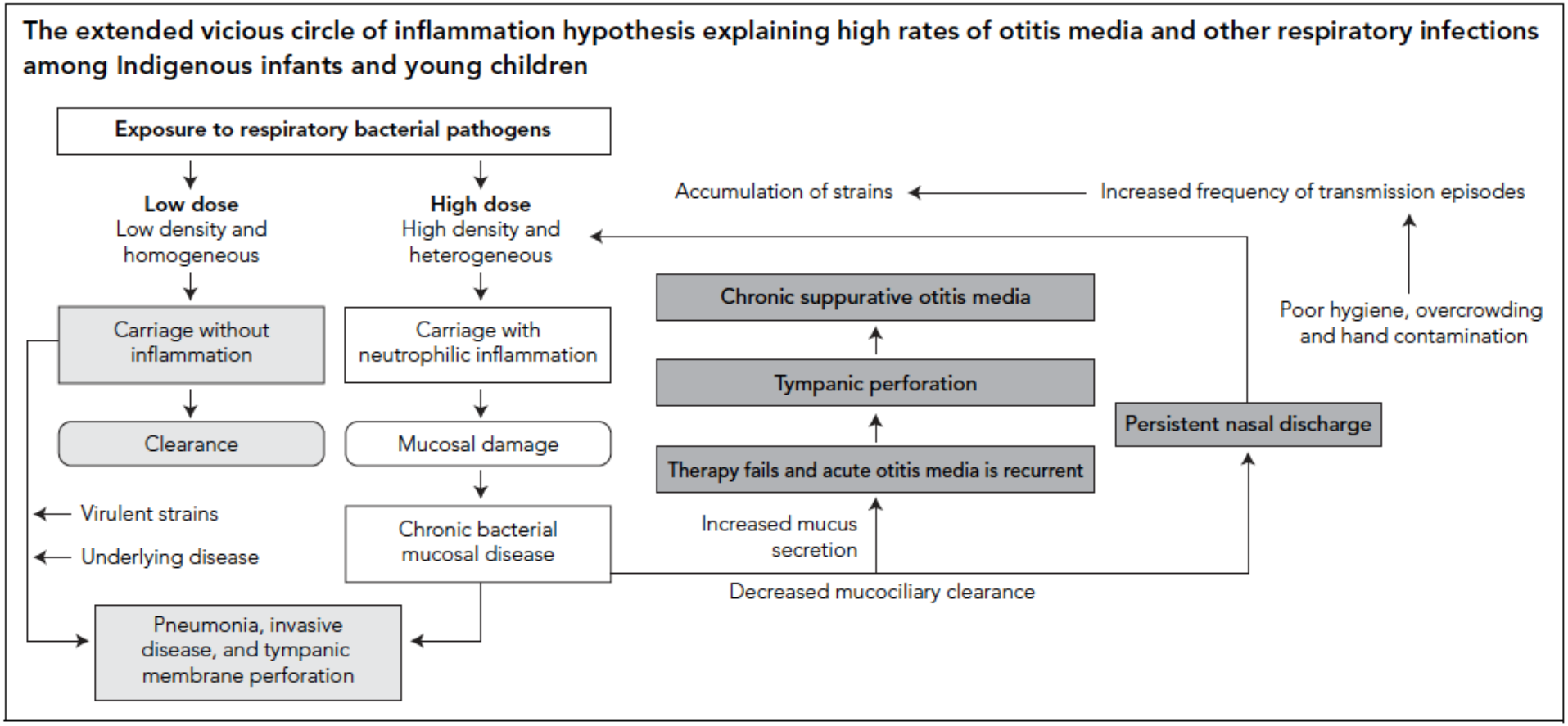
- 2 year follow-up, n=1214, associated with:
  - Bronchitis (OR 1.81 [1.2,2.7])
  - Urine infection (OR 1.94 [1.3,2.9])
  - Oral Herpes (OR 9.54 [3.3-27.3])
  - Pneumonia (OR 2.09 [0.92-4.76])

  Murphy EL, Arch Intern Med 1999, 159 (13): 1485-91

- Alice Springs Hospital, n=89 (58% HTLV-1 +)
  - Increased bronchiectasis, Cor pulmonale
  - Increased mortality (OR 5.78 [1.8-26.8]; P = .028)

  Einsiedel L, Clin Infect Dis. 2012 Jan 1;54(1):43-50.

Otitis Media



Immunological theories include: changes in innate immunity, TLRs,mannose-binding lectin and soluble CD14

Wiertsema, MJA 2009; 191, S50-4

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Scabies

- Scabies v Crusted Scabies
  - Housing overcrowding
  - Secondary bacterial infections

- Alterations
  - CD8 infiltration (rare CD20 / Macs)
  - Complement activation
  - Elevated IgG , median level twice normal
  - Innate

Walton S, Parasite Immunol 2010; 32: 532-40

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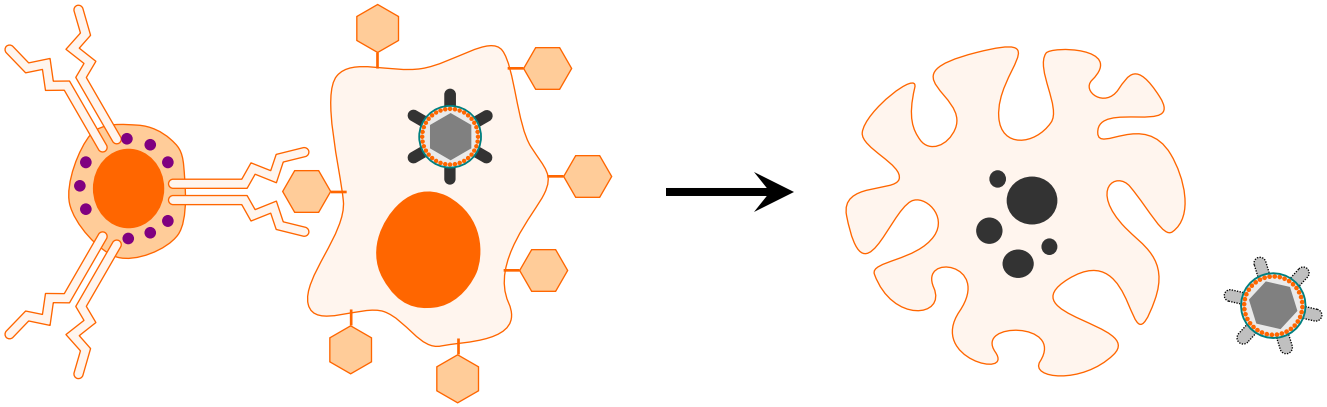
Clearance of Viral Infected Cells



Increased risk for CMV/ BK Virus risk is inversely related to absence of inhibitory KIR C ligand and the presence of activating KIR in the recipients – more activating KIR receptors (KIR3DS1) KIR B/X phenotype protective

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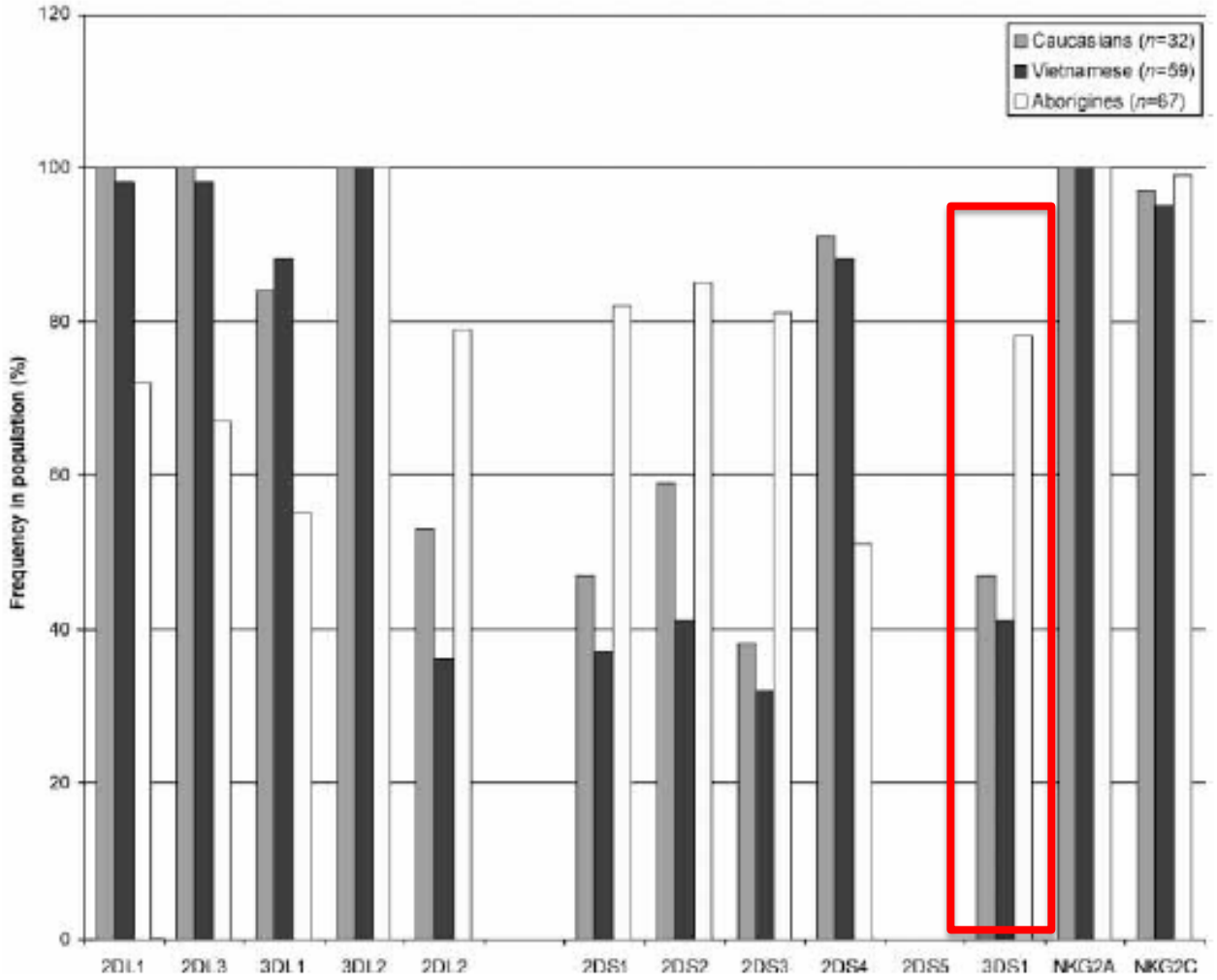
KIR Receptors in Vietnamese, Caucasians and Aboriginal Australians



KIR 3DS1

More likely KIR B/B or KIR B/X

Higher Activating KIR – should be more Protective!

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Exp
Transplantation

Toneva et al Tissue Antigens 2001

HLA in Aboriginal Australians

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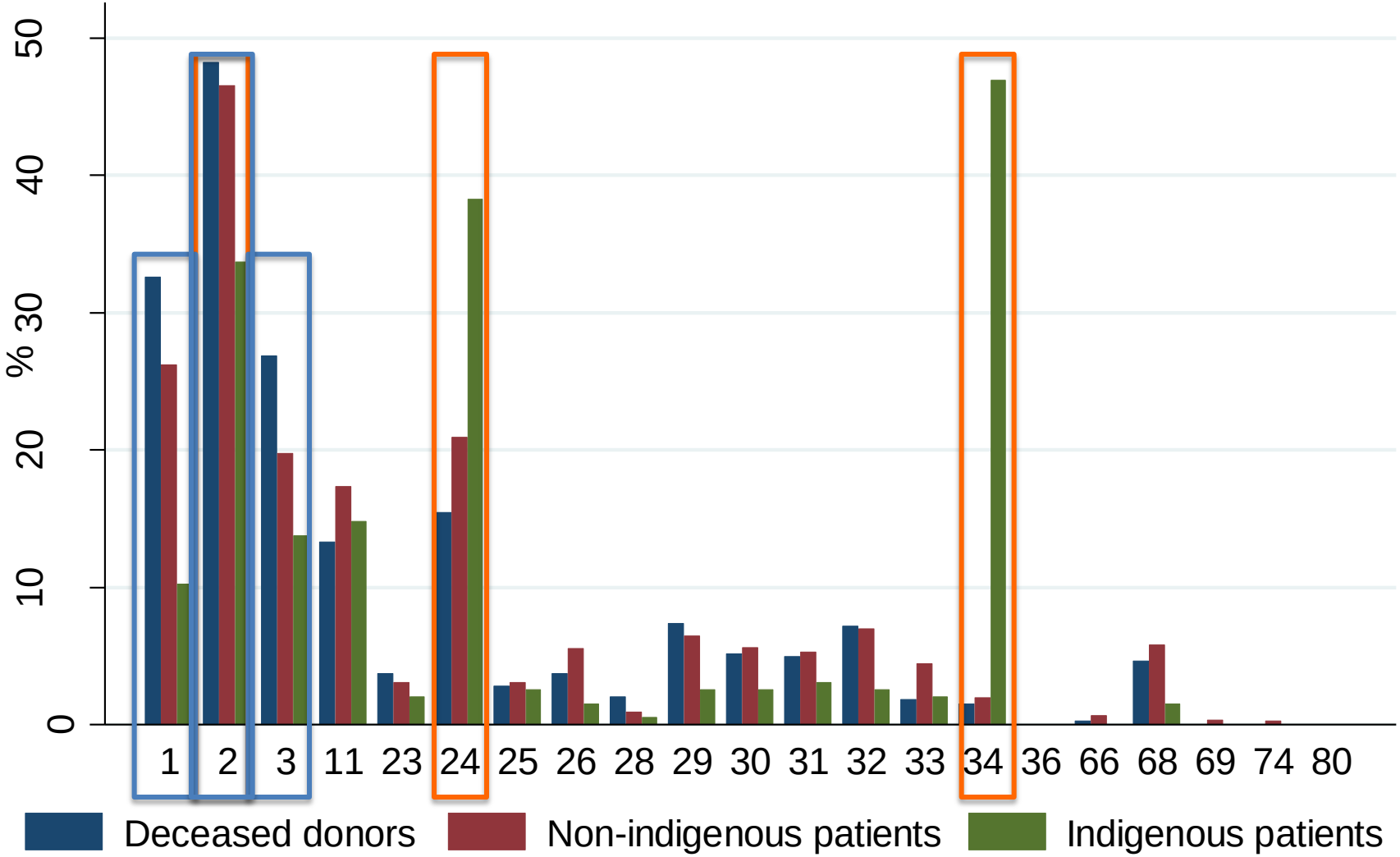
HLA-A distribution in Aboriginal Australians



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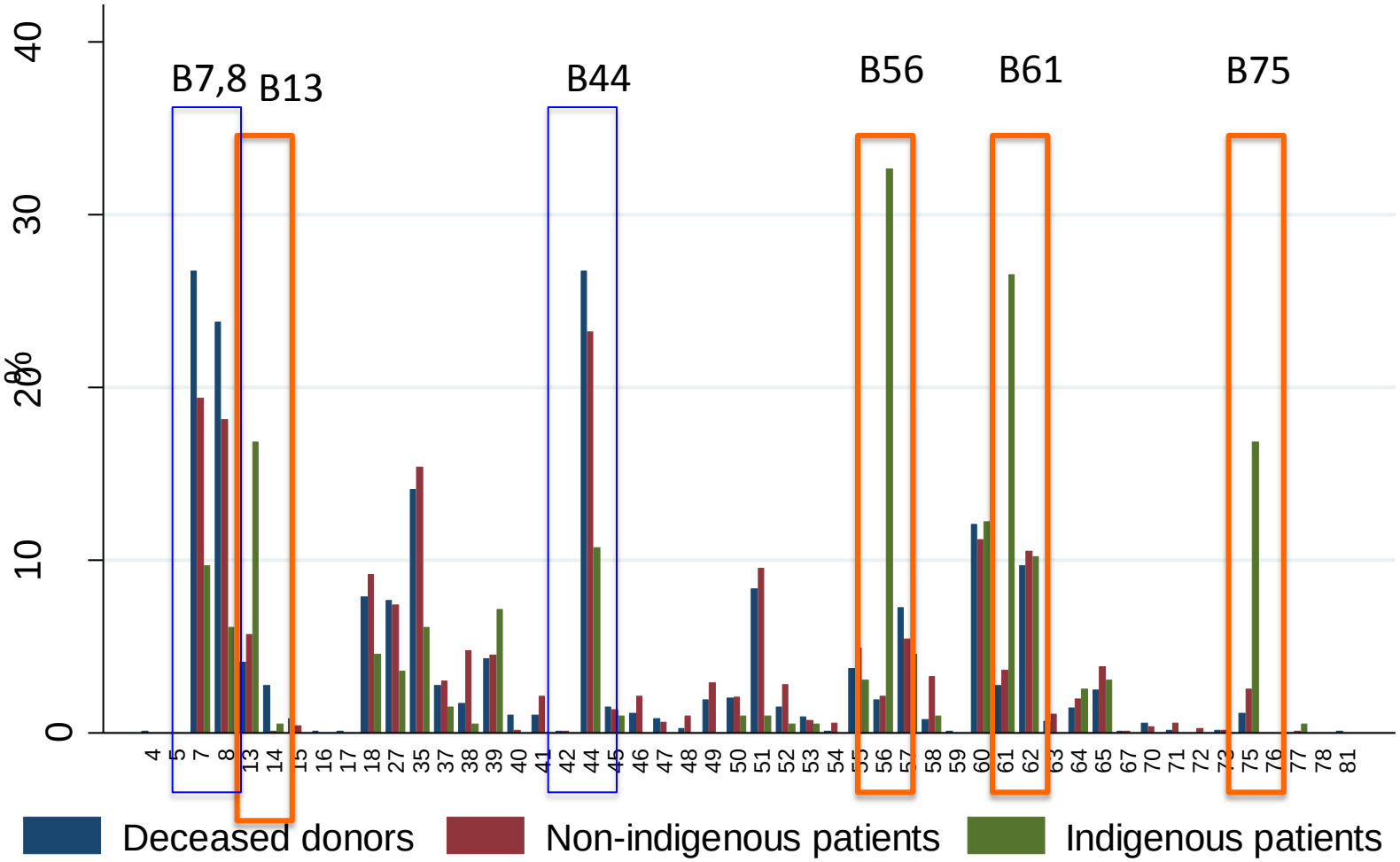
Australia 2006 - 2010

HLA-B distribution in Aboriginal Australians



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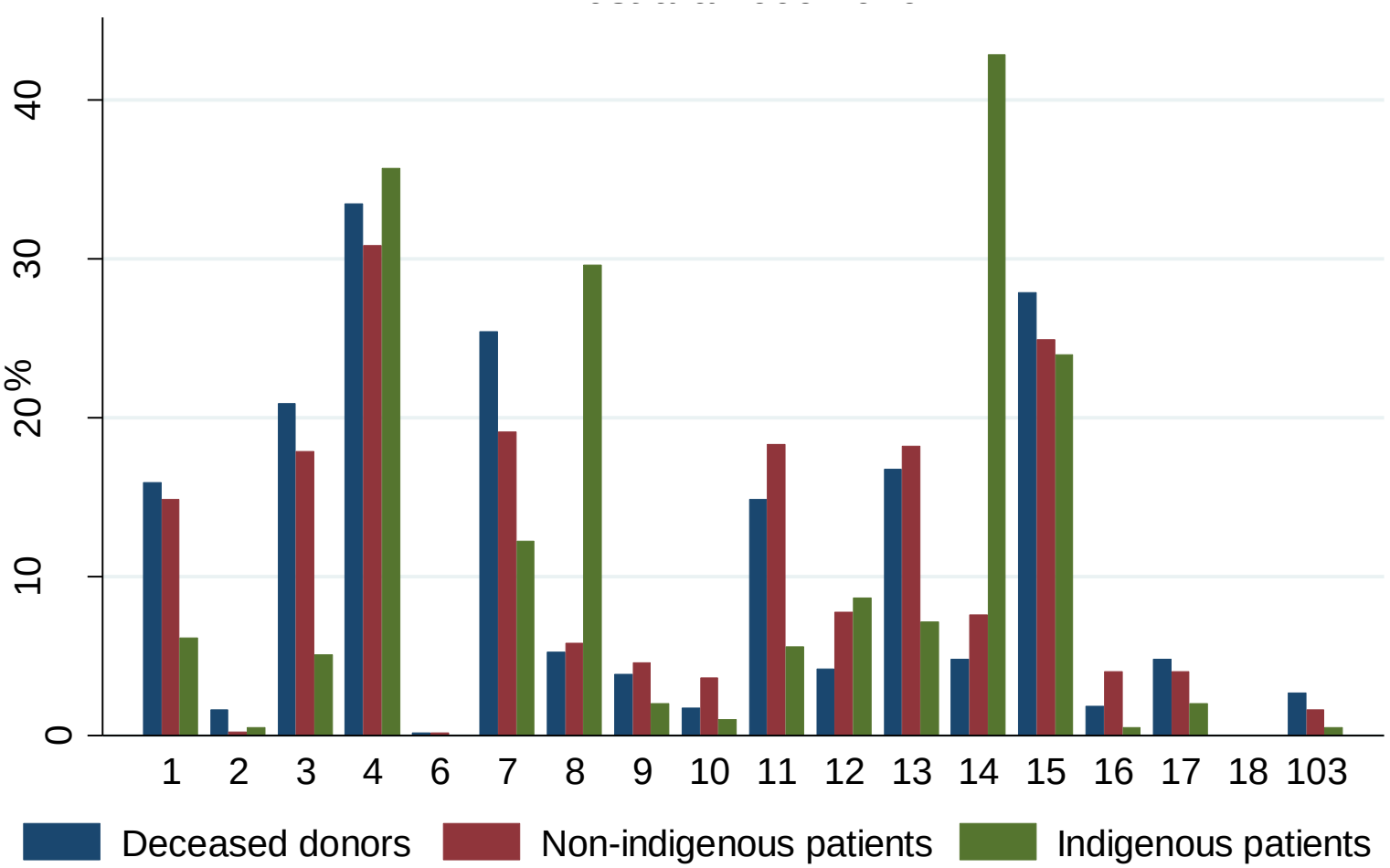
Australia 2006 - 2010

HLA Class I restricted polymorphism in Aboriginal Australians

- A locus: A*2, A*11, A*24, A*34
- B locus: B*13, B*62 , B*75,B*56, B*60, B*61
  - Caucasians B62 15:01 AA 15:25
  - Caucasians B75 15:02 AA 15:21
- C locus: Cw1, Cw3,Cw4, Cw7

HLA-DR distribution



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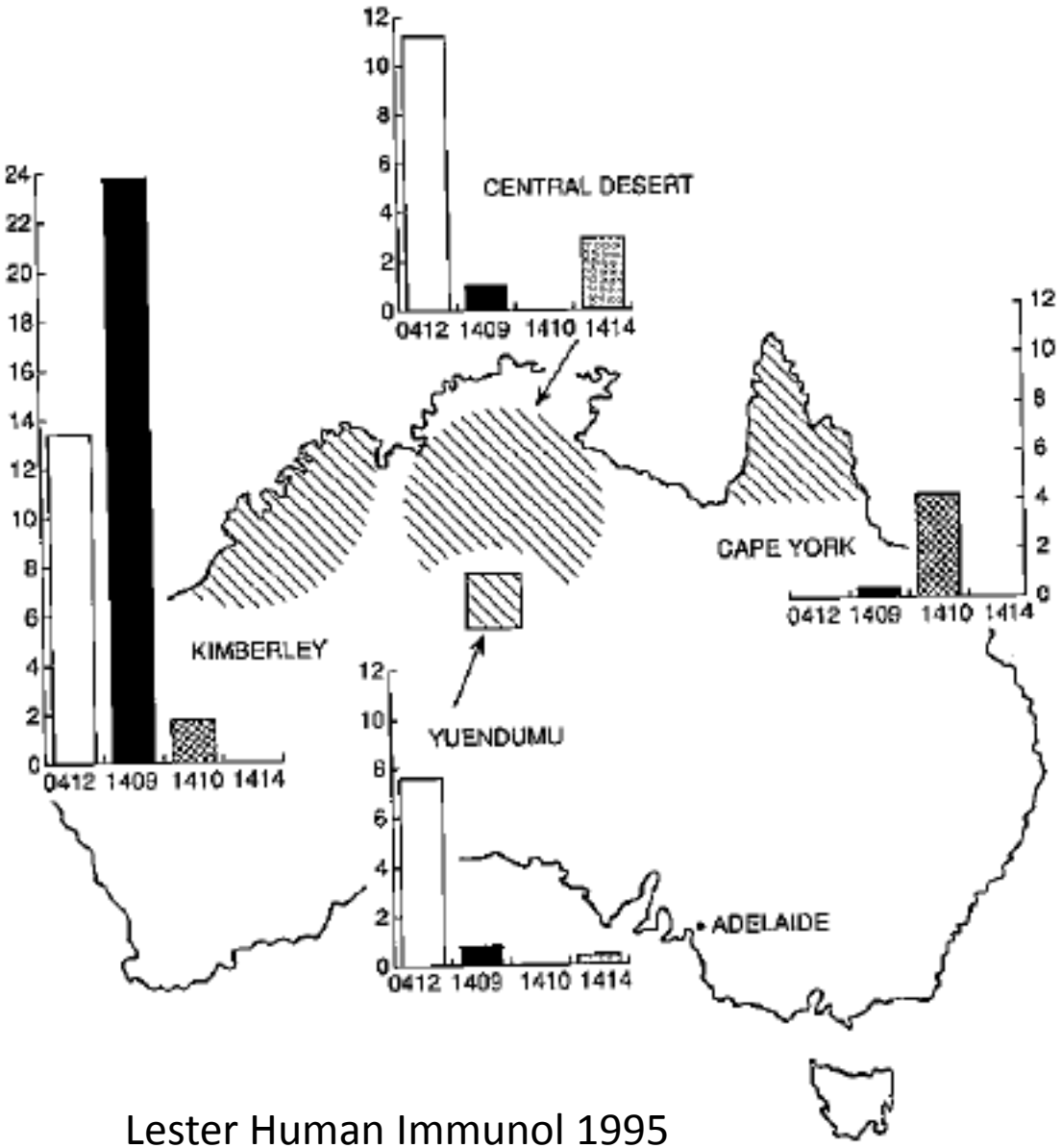
Australia 2006 - 2010

HLA-DR Alleles Across Australia in Aboriginal Australians



Lester Human Immunol 1995

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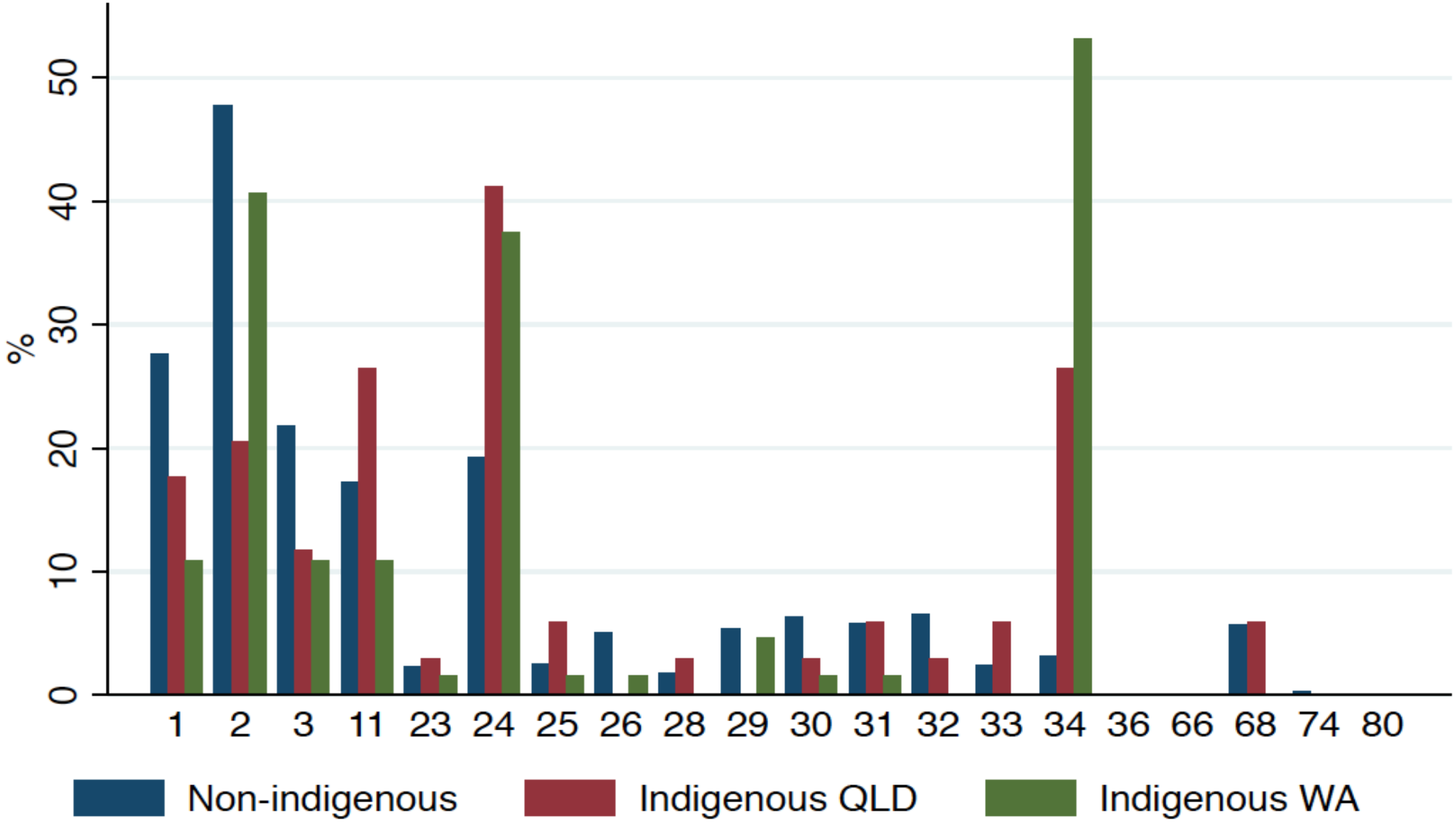
HLA-A distribution

Australia kidney waiting list 2006-2010



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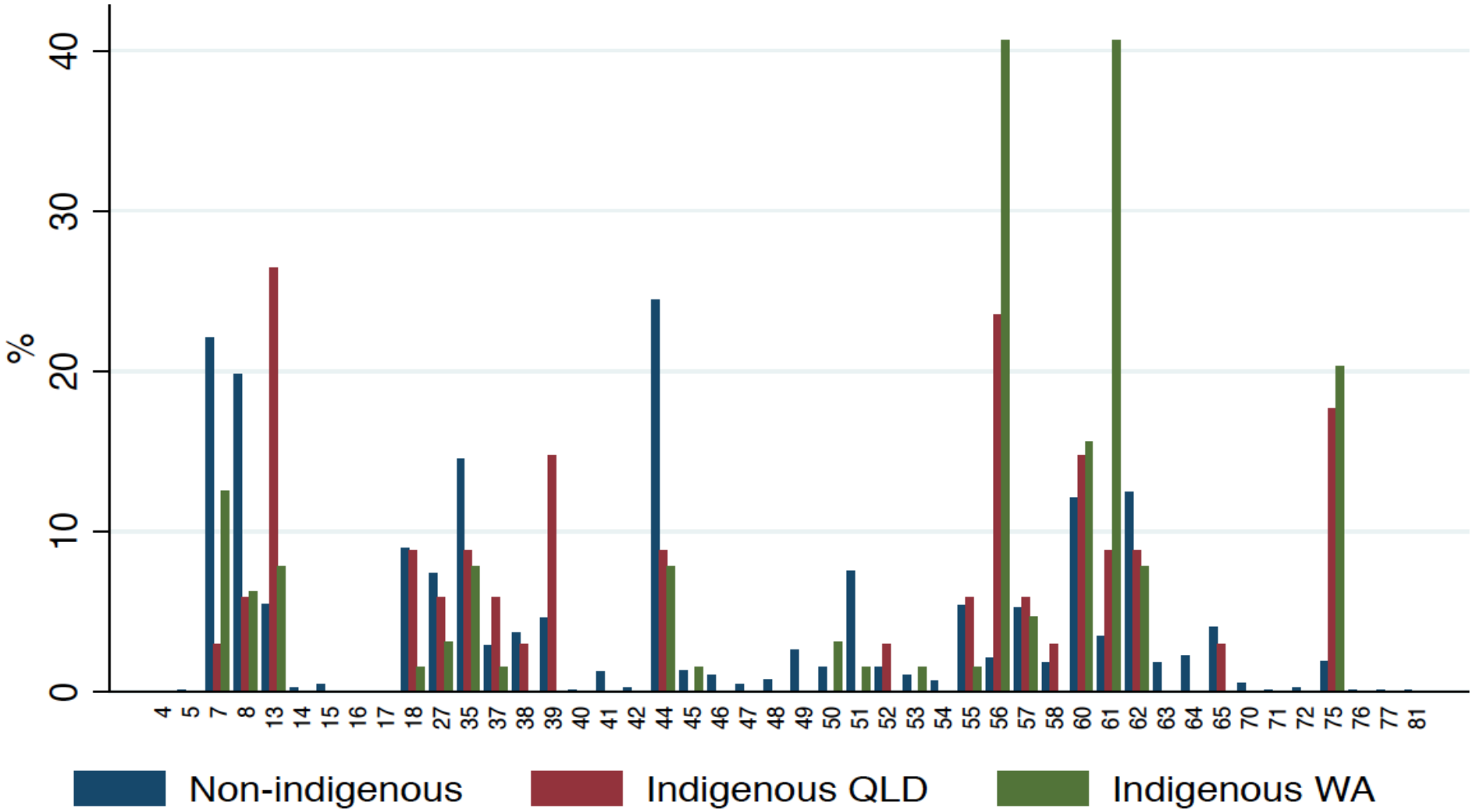
HLA-B distribution

Australia kidney waiting list 2006-2010



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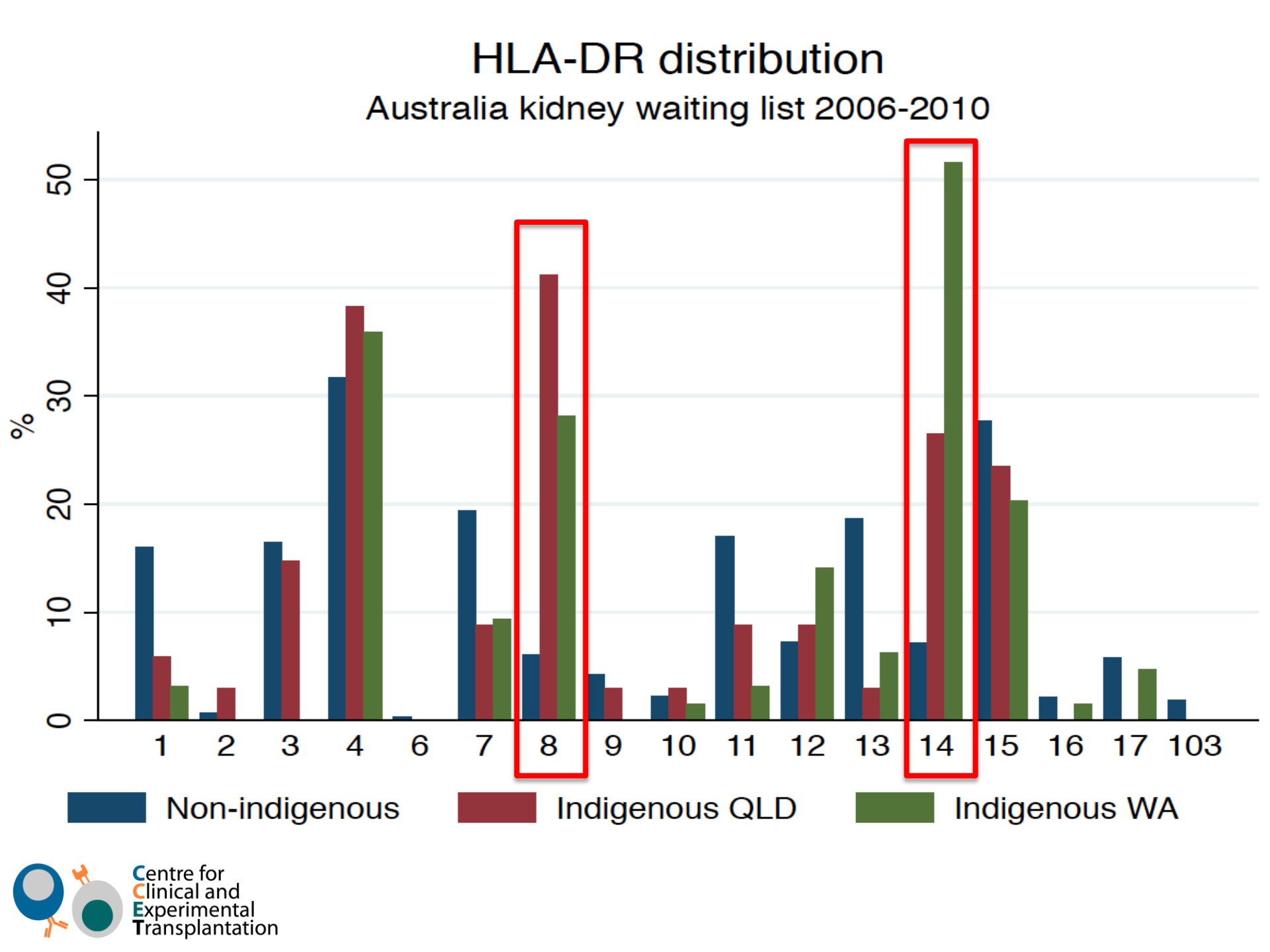

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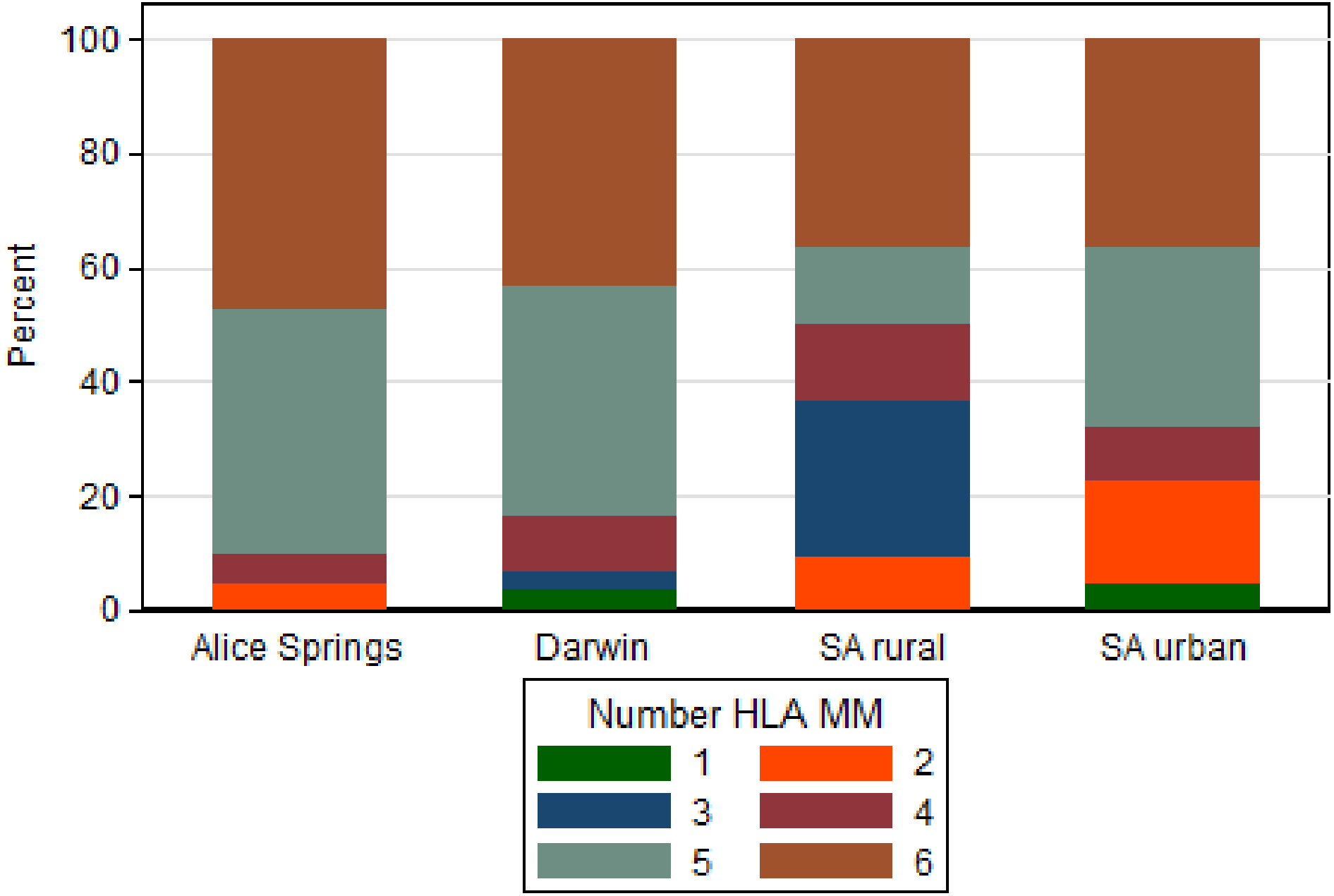
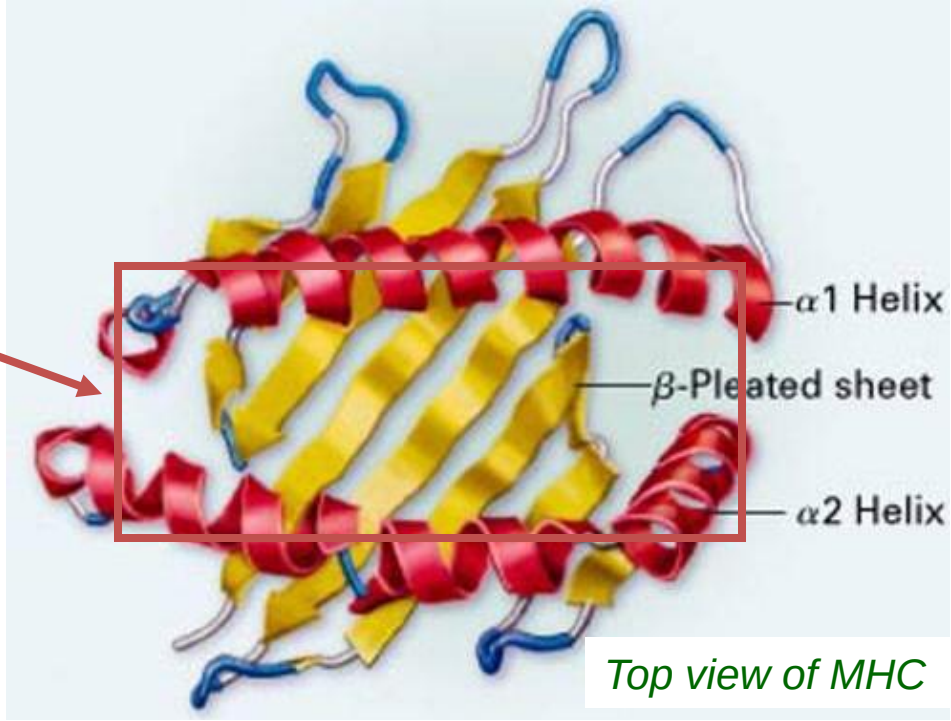


Indigenous recipients, SA / NT tx unit

Time to consider something different?

Polymorphism of Human Leukocyte Antigen (HLA) Class I and Class II Molecules

polymorphism is focused around the peptide binding region



Top view of MHC

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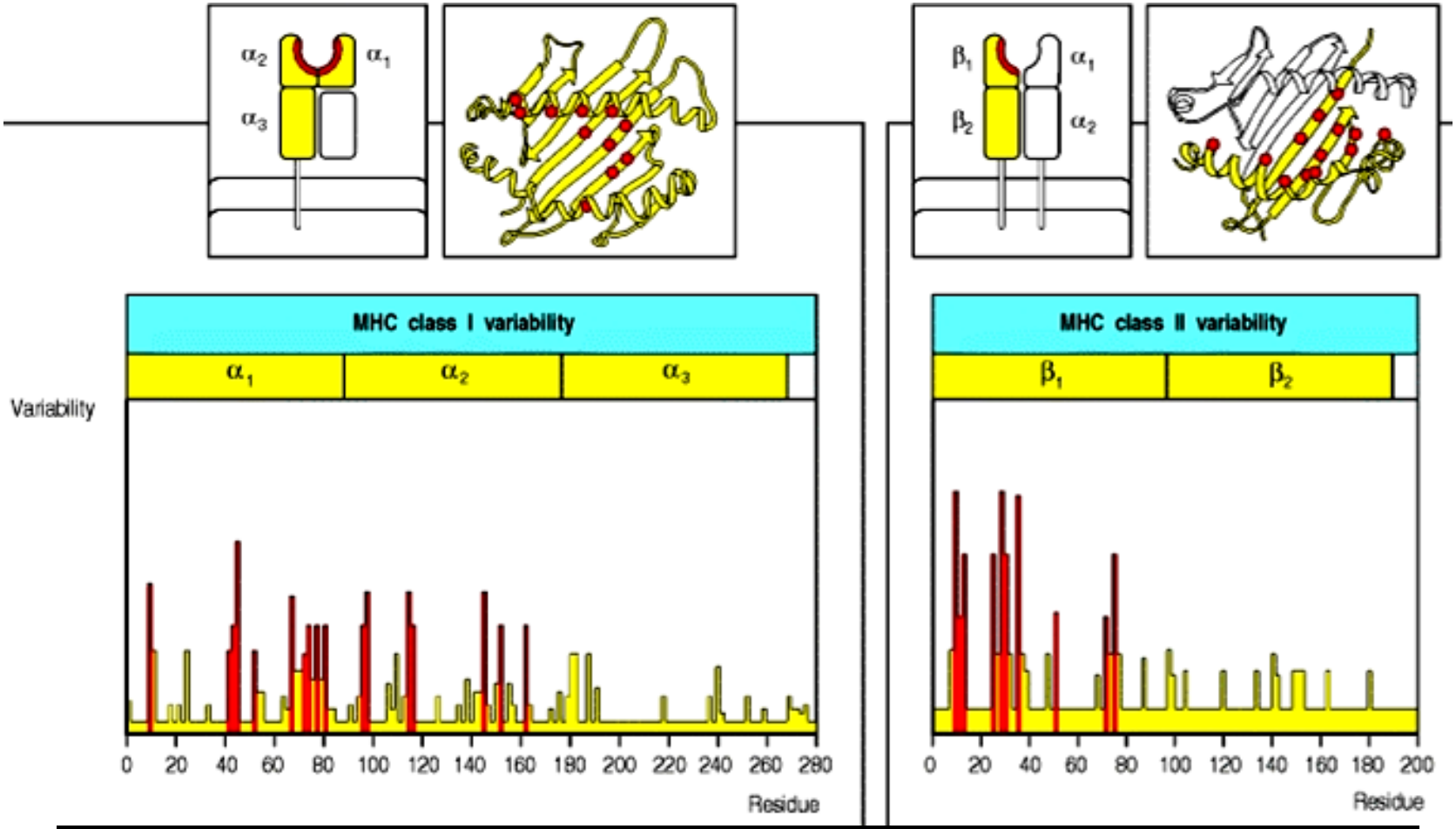
Polymorphisms within HLA molecules



Effects of the position of MHC polymorphisms:
-Different peptides presented by different MHC molecules

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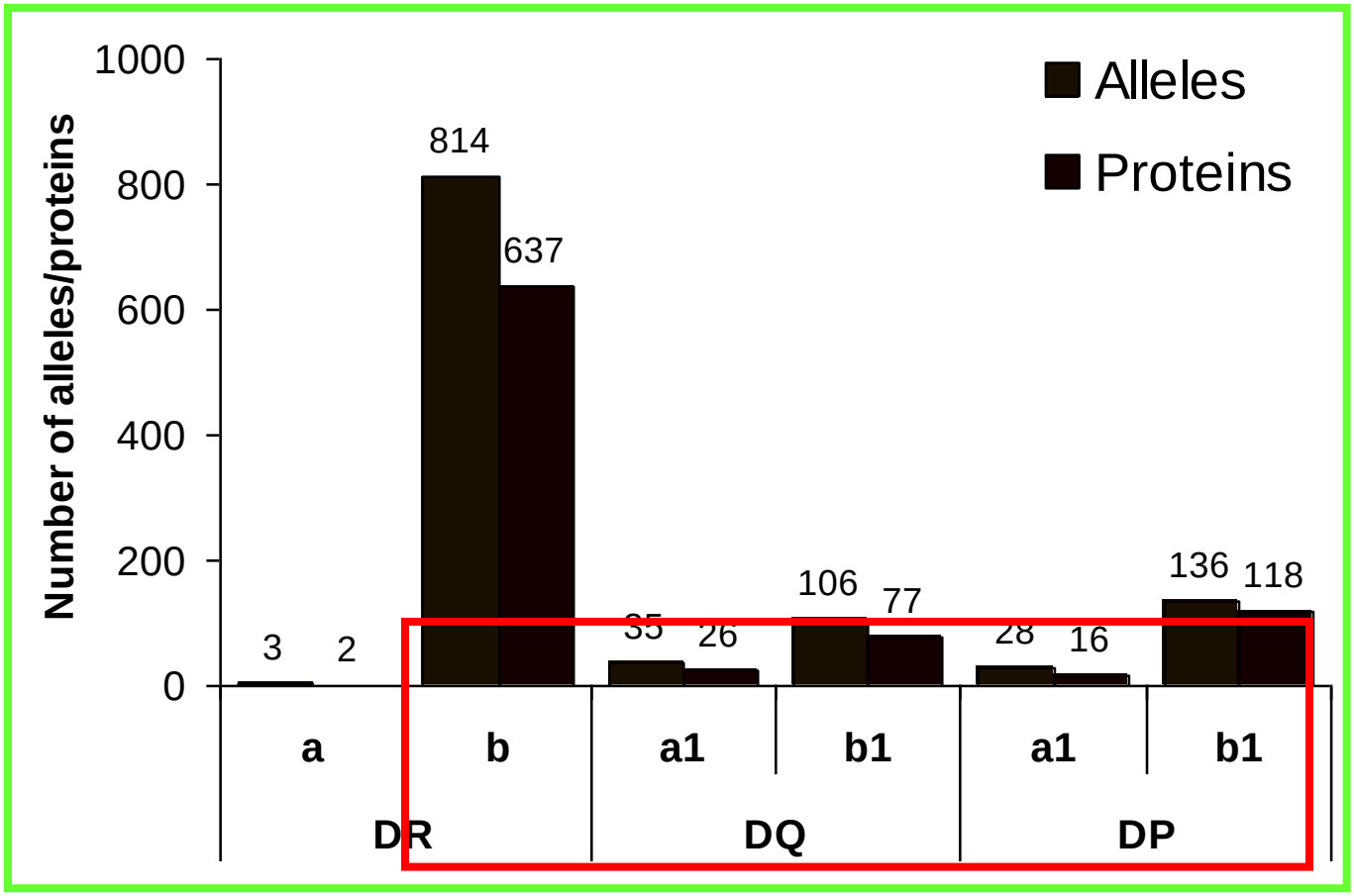
MHC Class II polymorphism



The most important HLA class II loci in transplantation are those with the largest number of alleles; HLA-DR β, -DQ β1, and –DP β1

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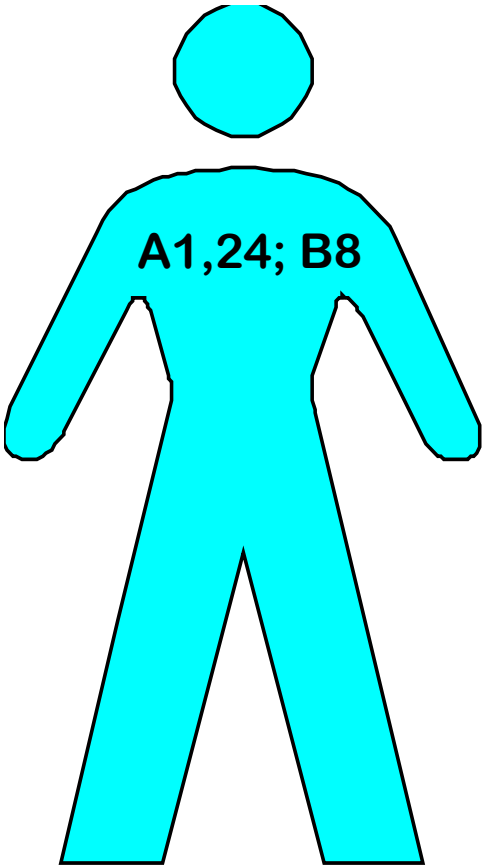
Generation of Donor Specific Antibodies (DSA)



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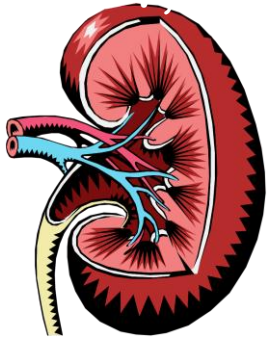

What antibodies are likely to develop?

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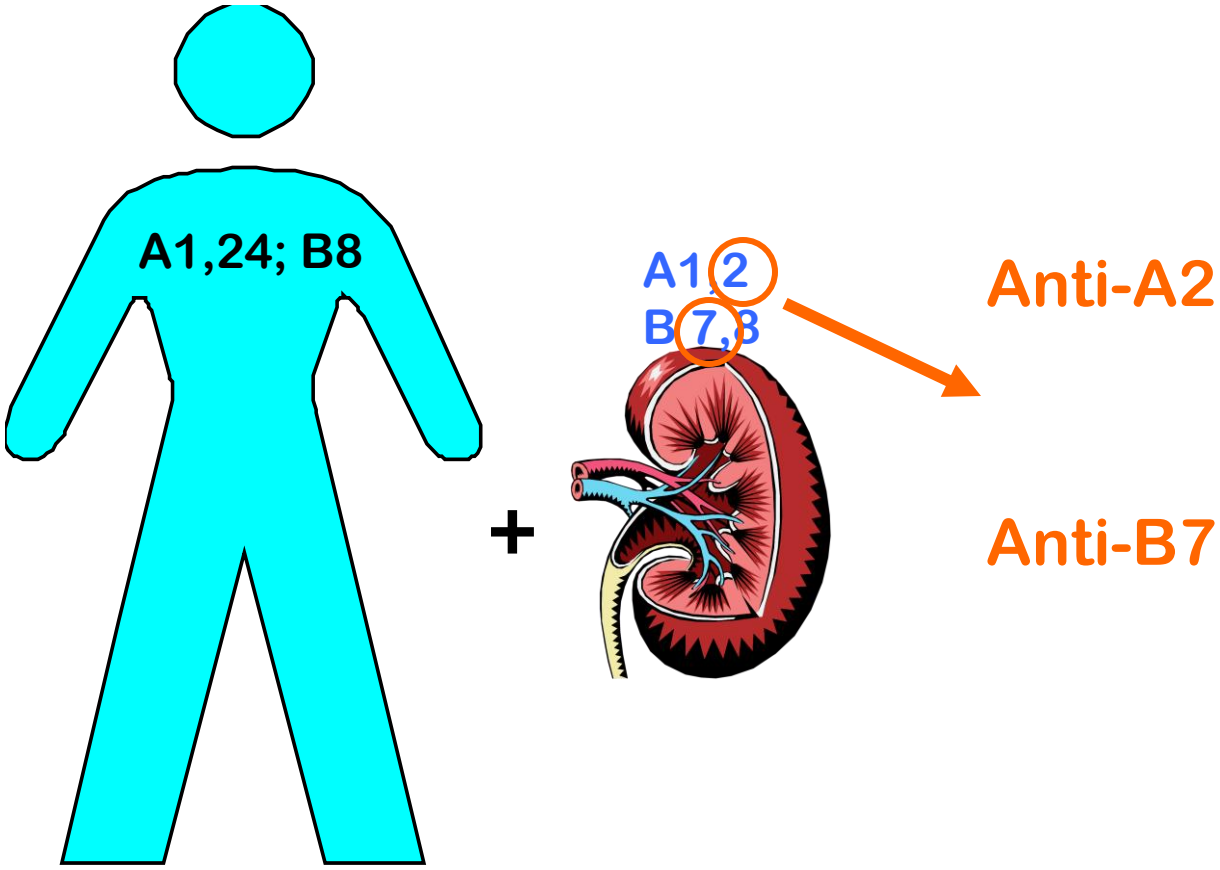
Generation of DSA



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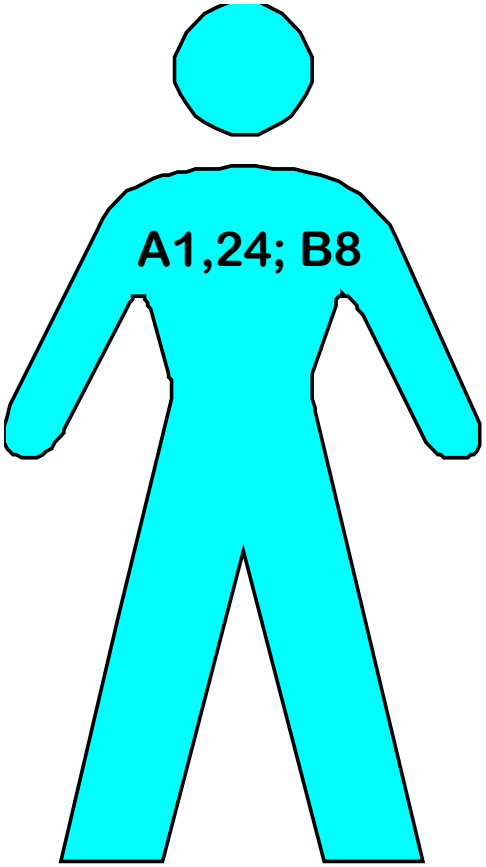
Generation of DSA

DSA rarely generated alone!



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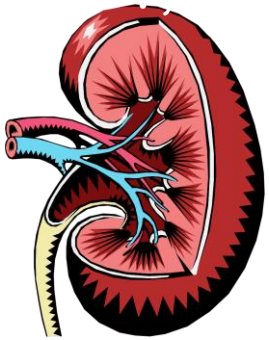

Anti A2

A68 A23 A28 B57 A69 B58 A24

Anti B7

B42 B55 B47 B13 B48 B27 B60 B61 B54 B41

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Due to shared epitopes with donor HLA

Epitope

- Part of a protein made up of amino acids that is recognized by the immune system
  - Linear epitopes – sequences of amino acids
    - For HLA molecules these are ***triplet*** of amino acids
  - Conformation epitopes – non contiguous amino acids sequence recognized by the immune system
    - For HLA molecules these are called ***eplets***

Eplets

Most eplets are triplets but not all

EPITOPE + TRIPLET = EPLET

HLA matchmaker

- HLA-Matchmaker is a computer algorithm to determine structurally based HLA compatibility and to identify acceptable HLA mismatches for highly sensitized patients

Identification of Antibody-Defined Epitopes from Amino Acid Polymorphisms

Two groups of polymorphic amino acids

1. Surface residues accessible to antibody
2. Hidden residues that cannot make direct contact with antibody

Identification of Antibody-Defined Epitopes from Amino Acid Polymorphisms

Two groups of polymorphic amino acids

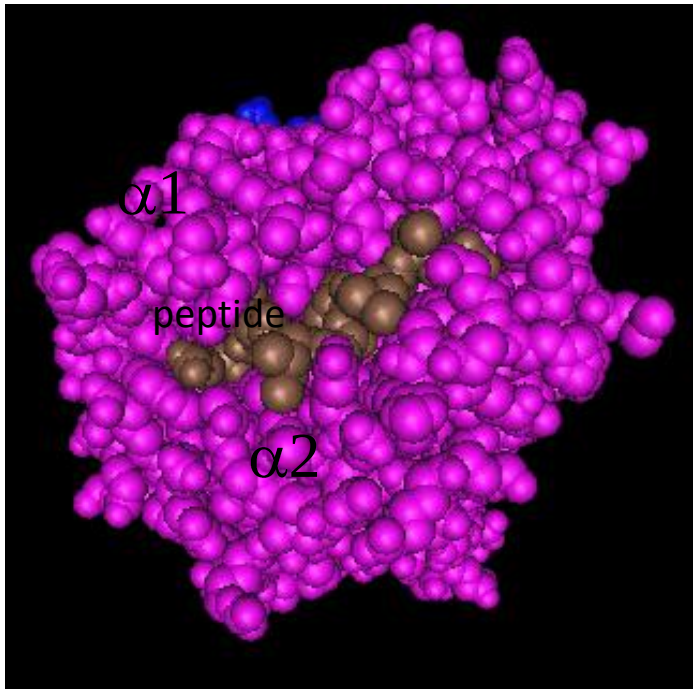
Surface residues accessible to antibody

Hidden residues that cannot make direct contact with antibody

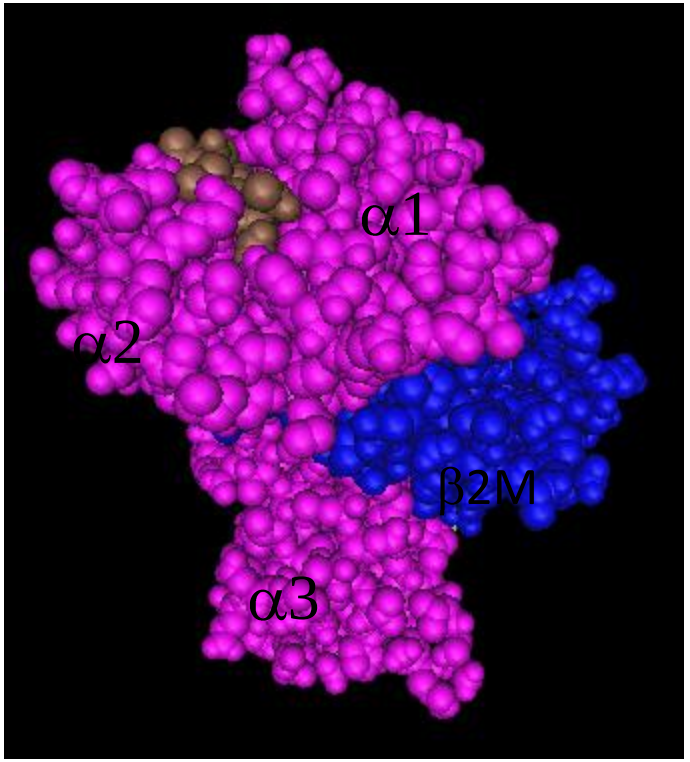
Three-dimensional structural modeling of HLA molecules with Cn3D (NCBI) and Geno3D (Combet et al, 2002)

Structural Polymorphism of HLA

Where do we “see” the polymorphic residues?



Top view



Side view

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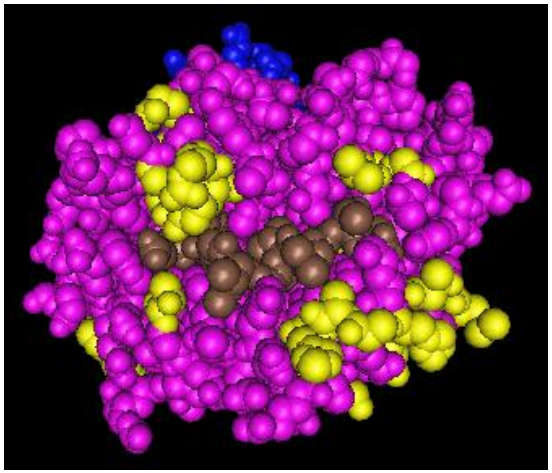
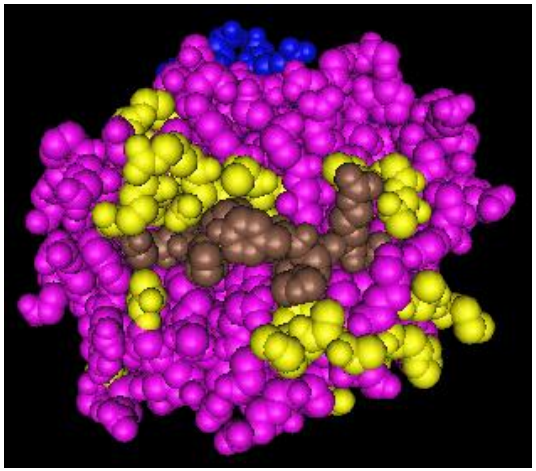
Top View of Exposed Polymorphic Residues

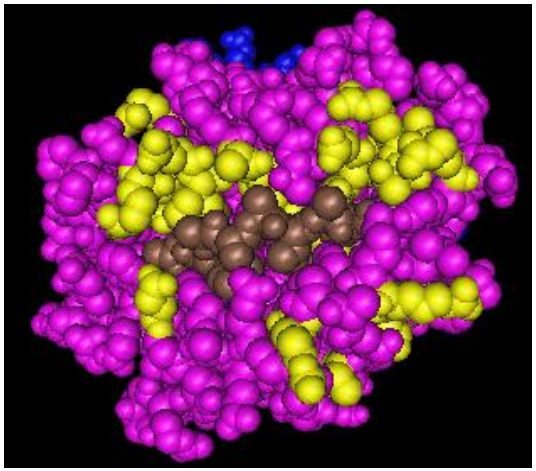
HLA-A2



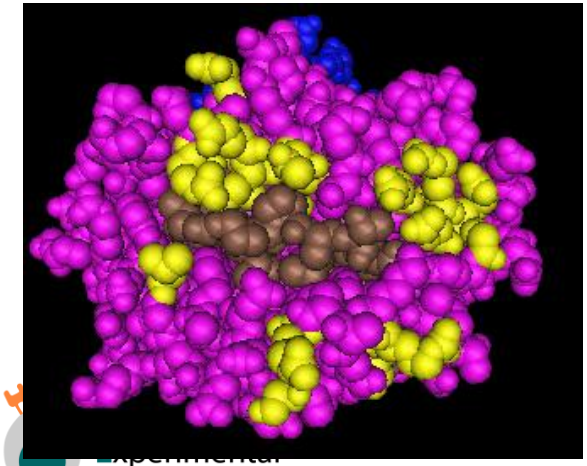
HLA-A68



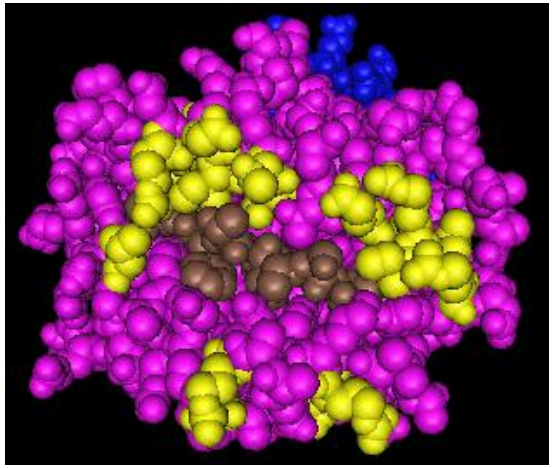
HLA-B27



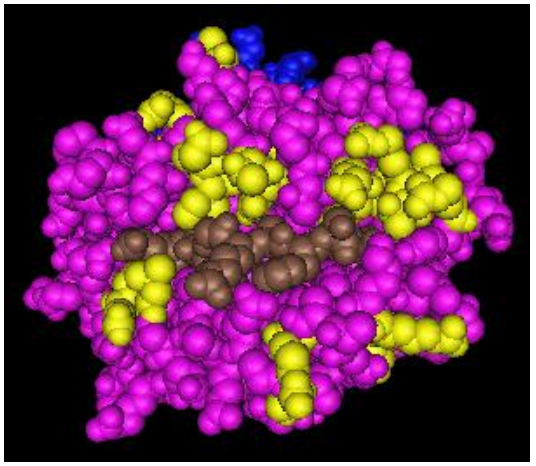
HLA-B35



HLA-B51

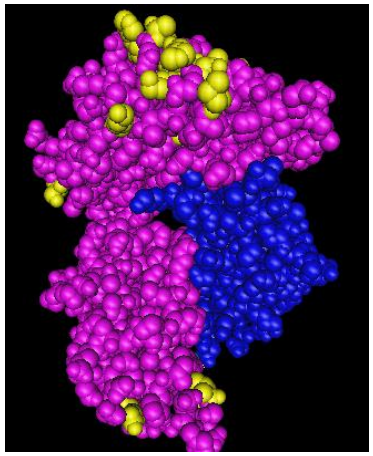
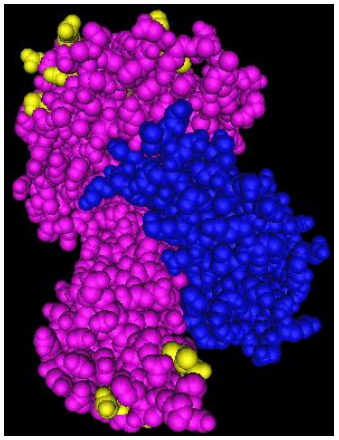
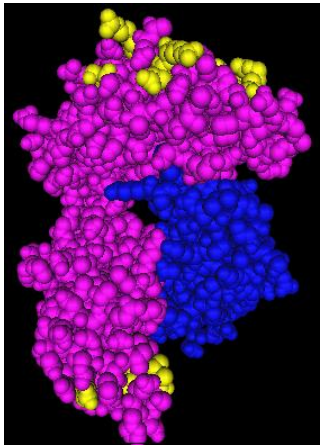
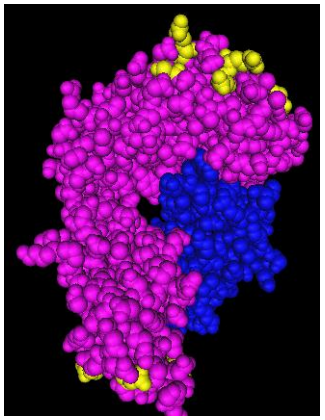
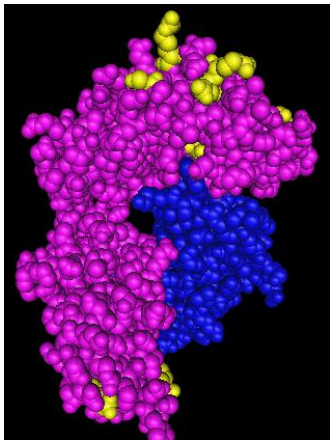
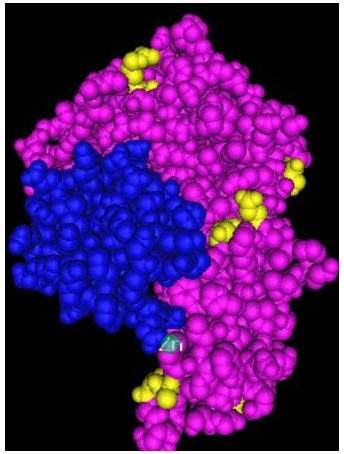
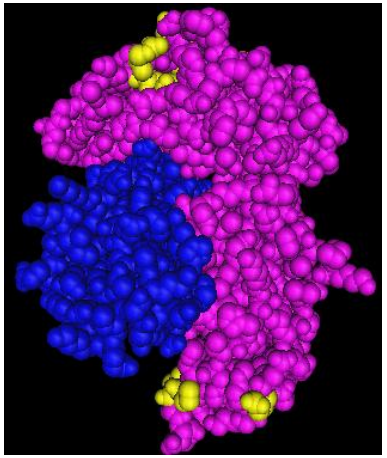
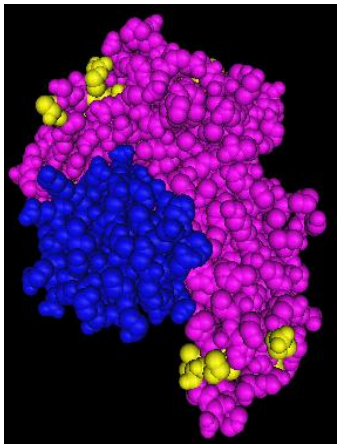
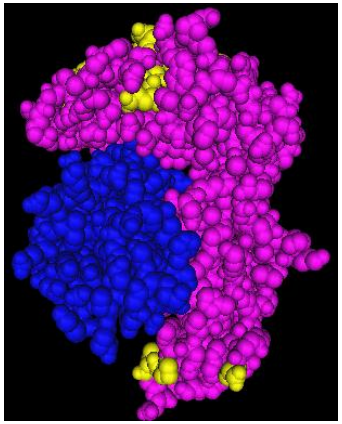
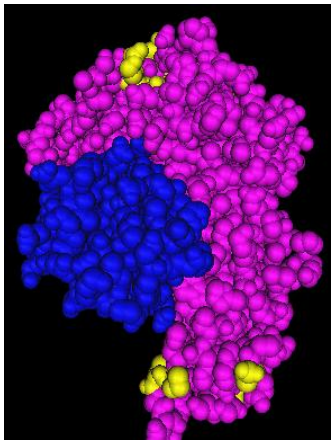


HLA-B44



Exposed Polymorphic Residues on the Sides of HLA molecules

HLA-A2 HLA-B27 HLA-B44 HLA-B51 HLA-B35

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Hidden Polymorphic Amino Acid Residues

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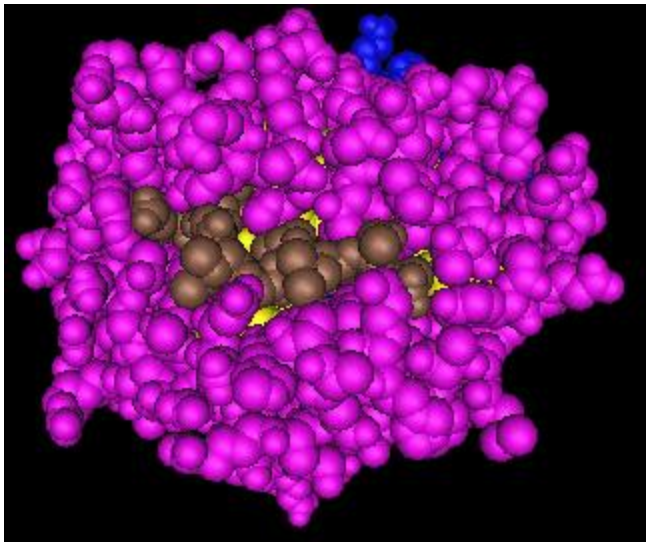
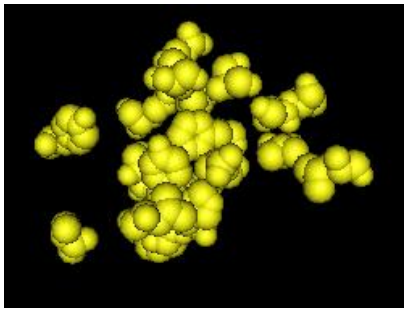
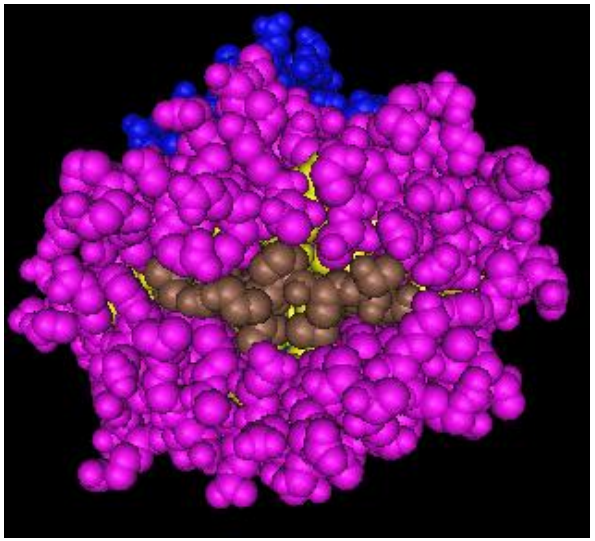
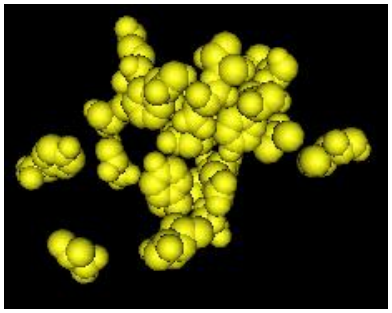




B*3501





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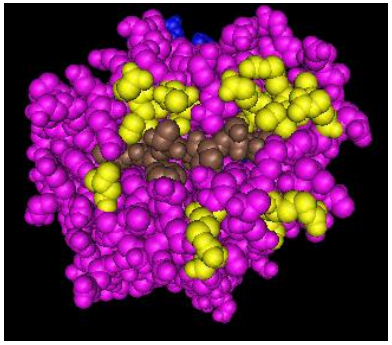
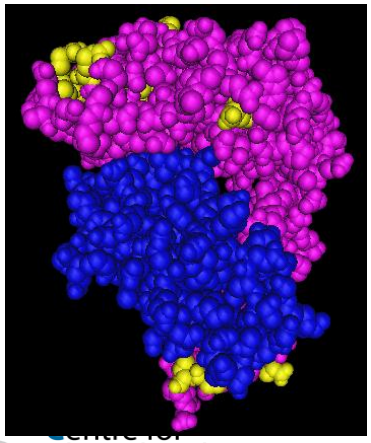
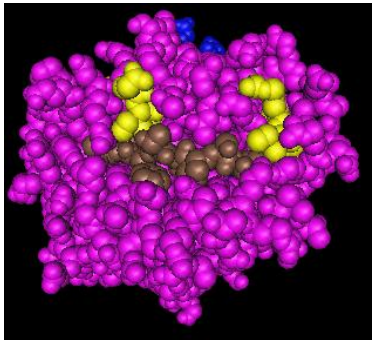
Structural Basis of a HLA-B51 Mismatch

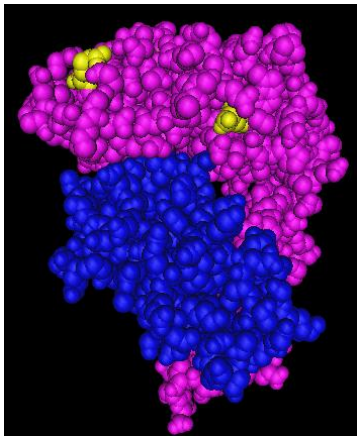
Polymorphic Residues on B51





"Seen" by A2,A68; B27,B44





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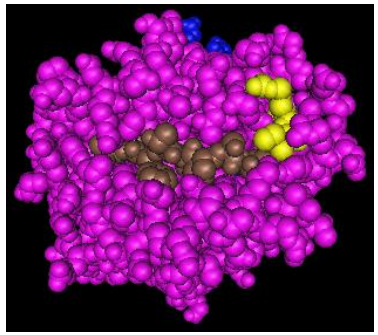
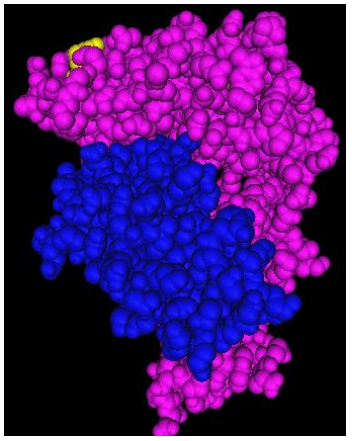
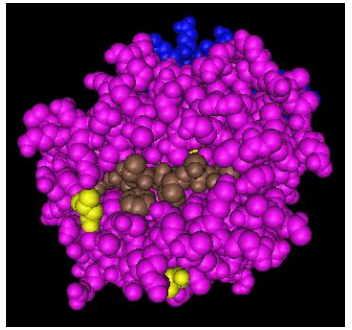
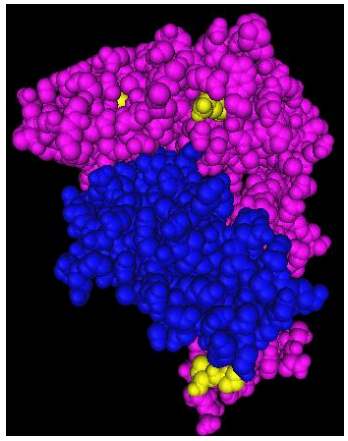


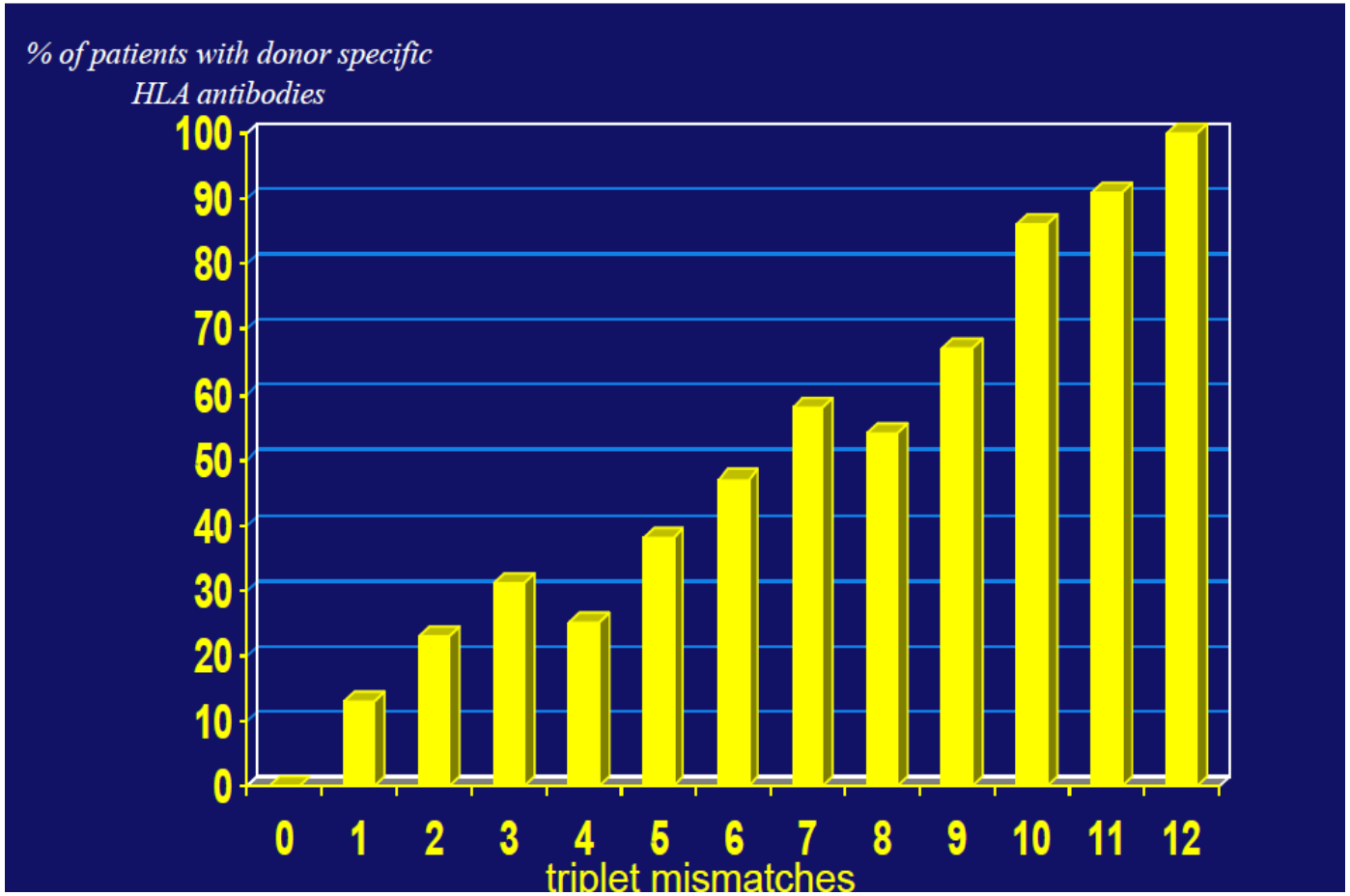


"Seen" by A2,A24; B7,B8





The number of triplet mismatches predicts HLA antibody production after renal allograft rejection



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(Courtesy Frans Claas)

OK – so what? Few AA patients make it to second transplant does any of this really matter at all?

HLA and Eplet mismatch in deceased donor renal transplantation

- *Patient Cohort*

  - 590 patients transplanted 2004-2009

  - Donors were from Victoria.

- *HLA genotyping*

  - *Donors HLA typed in Victoria..*

  - *eplet mismatching calculated accordingly using MatchMaker.*

- *Clinical Data*

  - Clinical data including rejection history and biopsy results were obtained from the ANZDATA database.

Brian Tait VTIS

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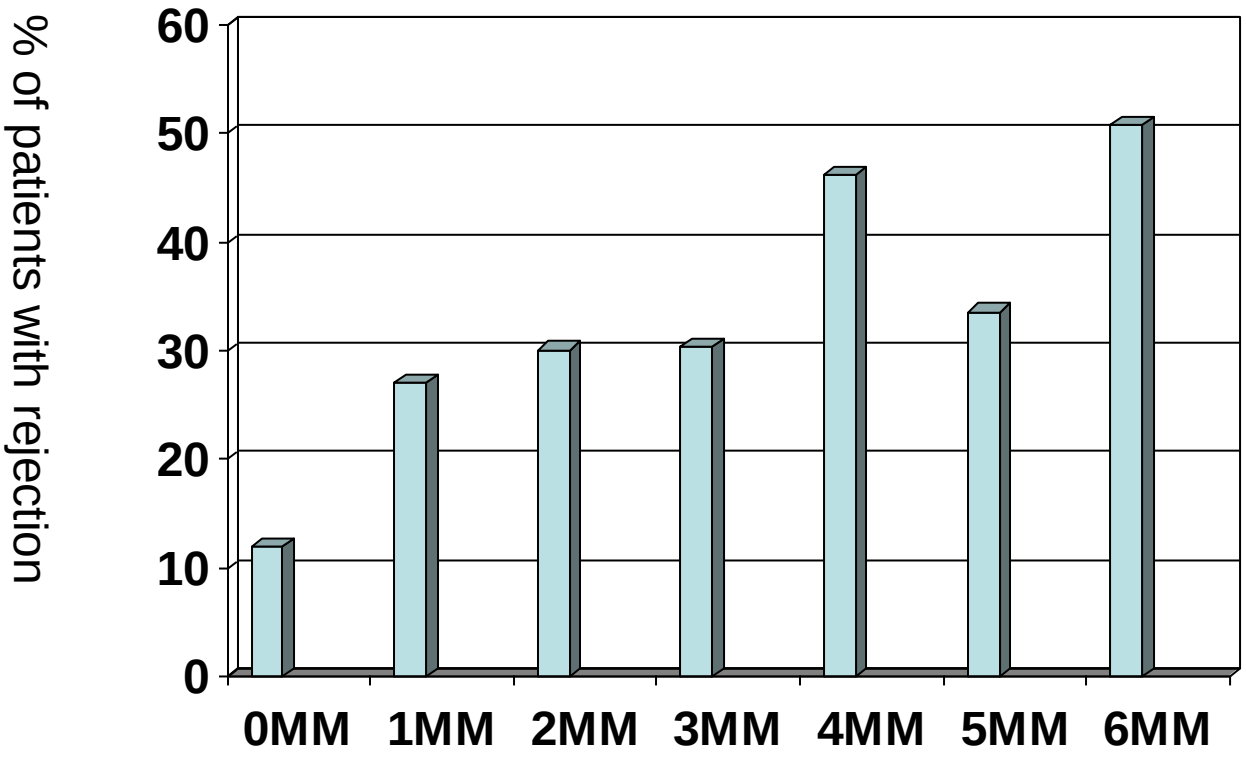
High level of HLA mismatch increases risk of cellular/humoral rejection



0,1,2 MM
versus 4,5,6 MM
P<0.005

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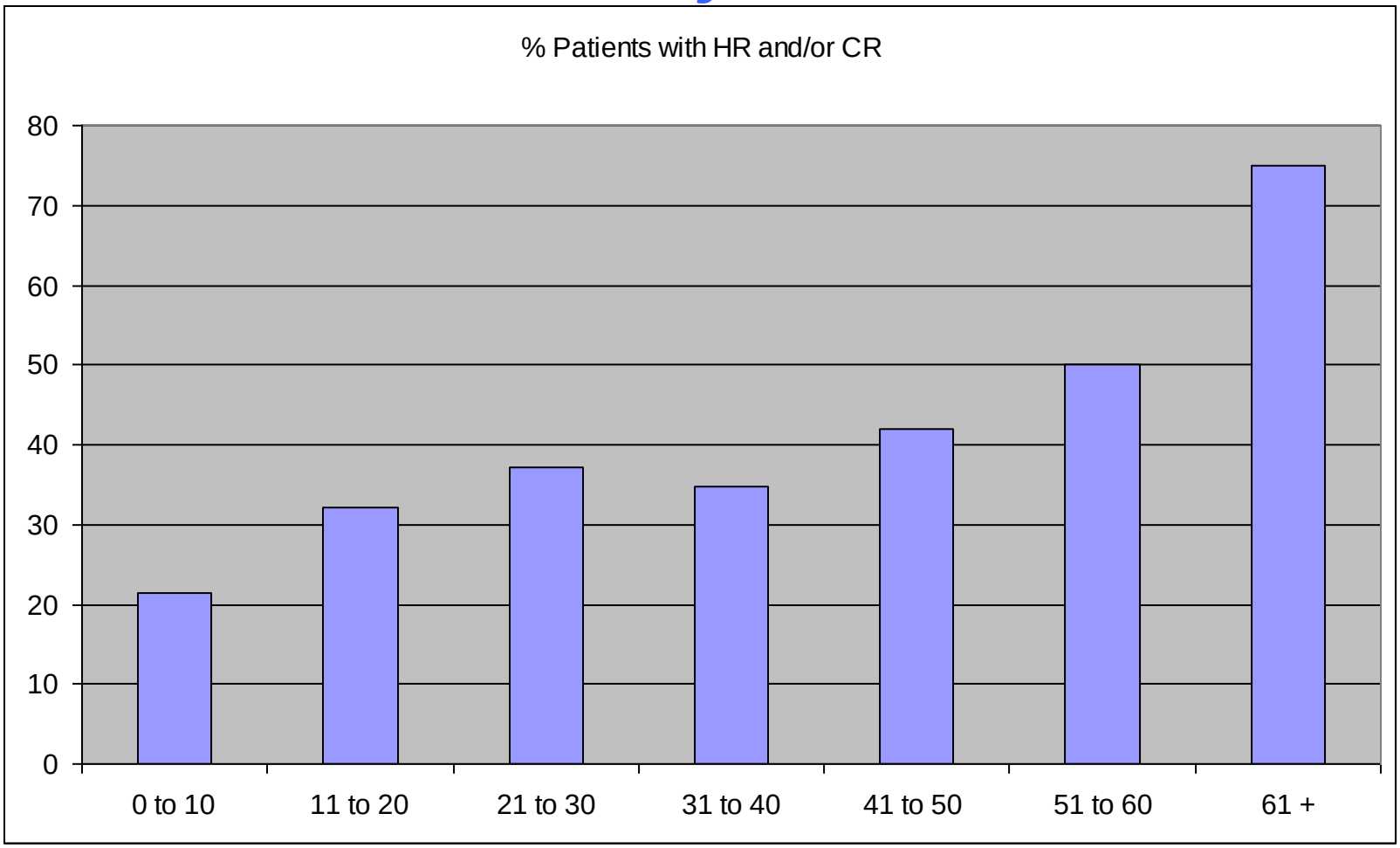
High level of Eplet mismatch increases risk of rejection



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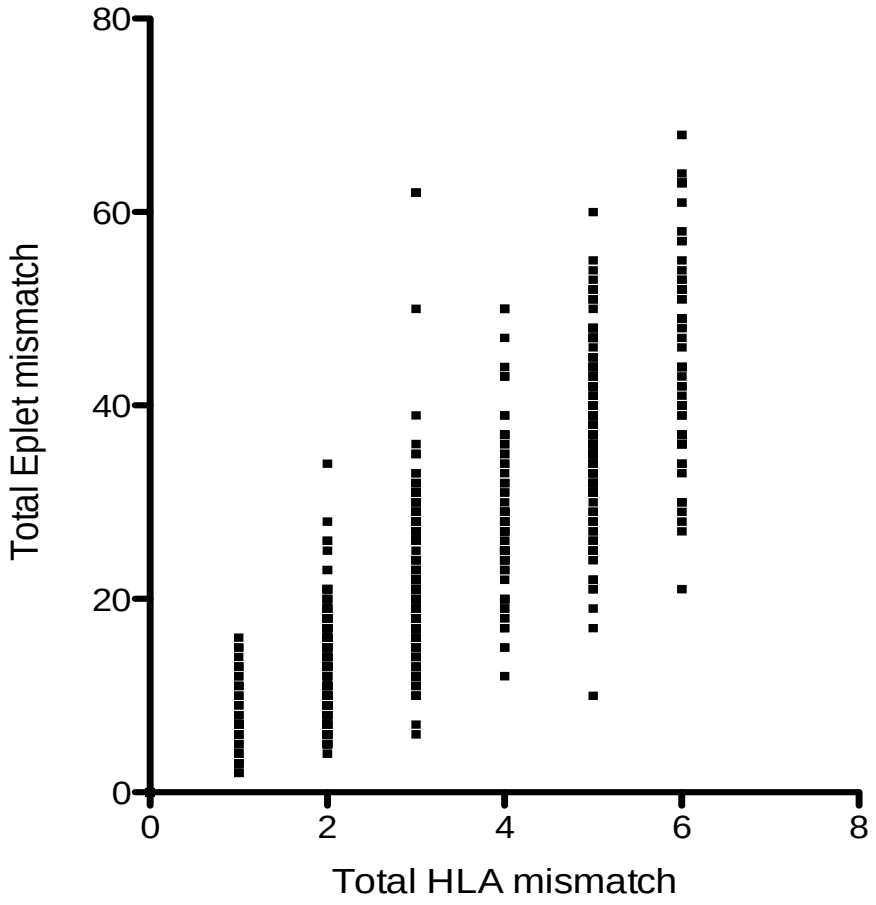
0-30 eMM v 41+eMM
P<0.0001

HLA mismatch can have wide variation in Eplet mismatch



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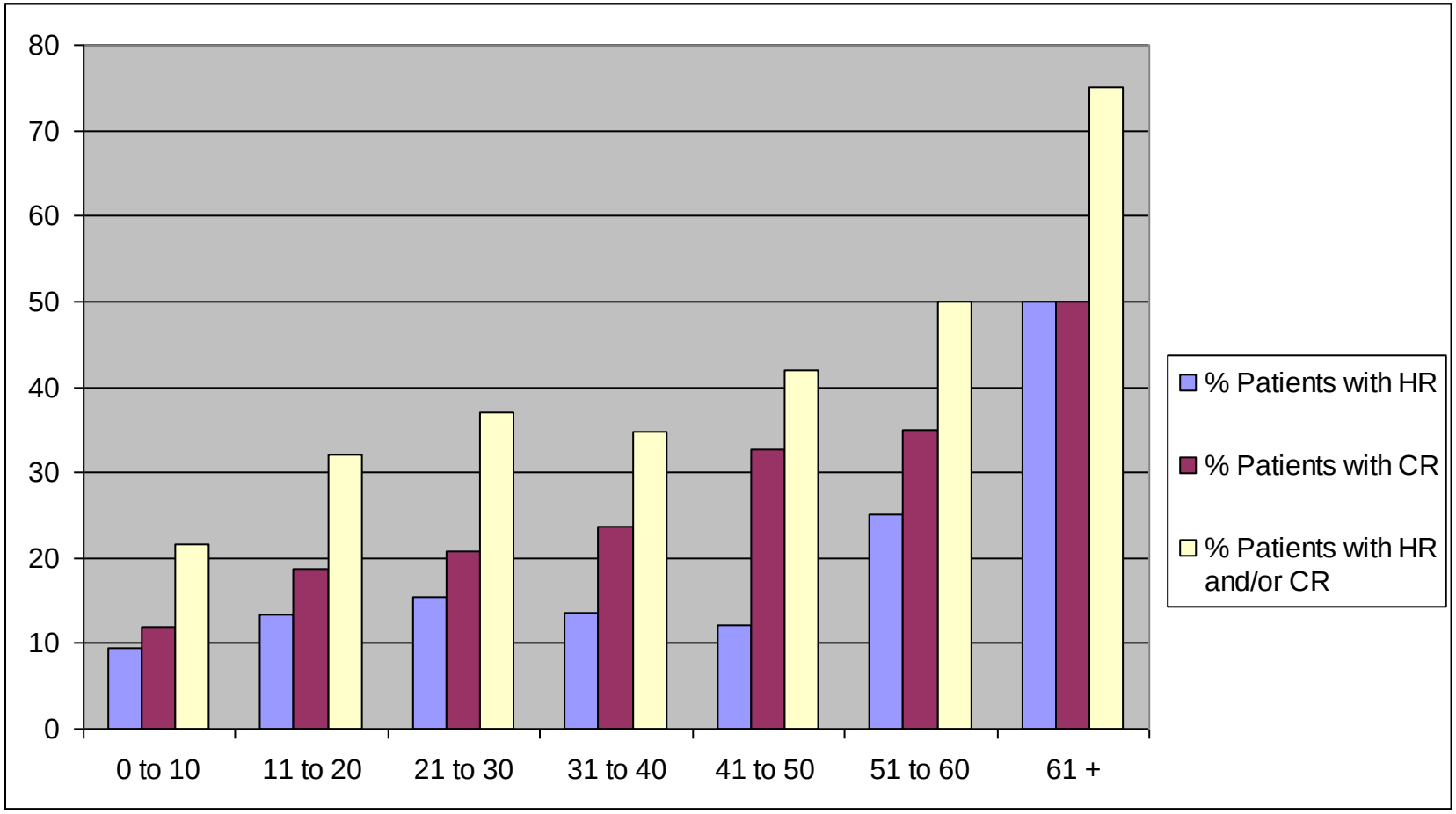
Eplet mismatches and type of rejection



HR=humoral rejection
CR=cellular rejection

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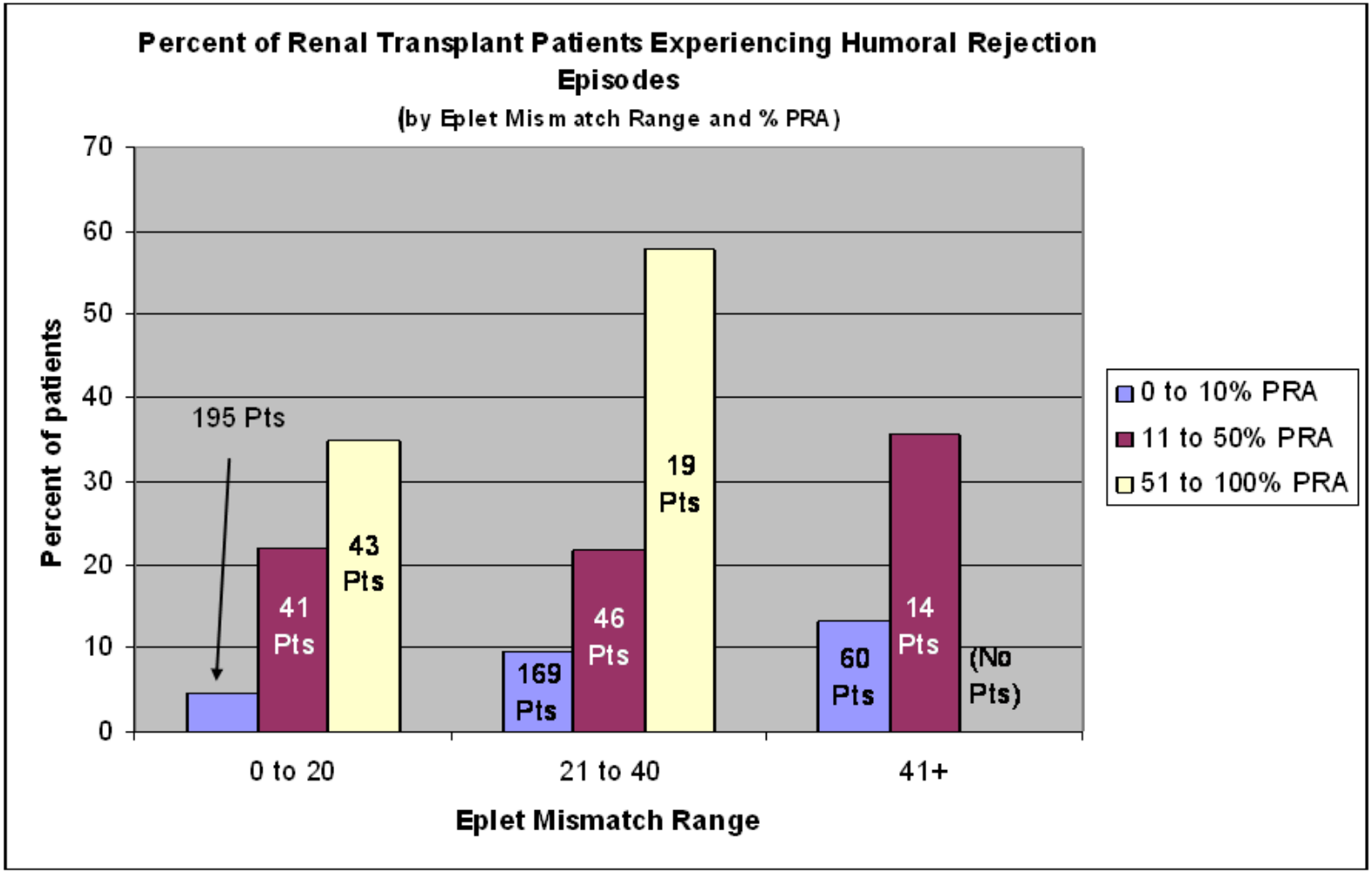
HR p=NS
CR p<0.001 (0-20 eMM v 40+ eMM)

Rejection risk is compounded by PRA levels and Eplet mismatch



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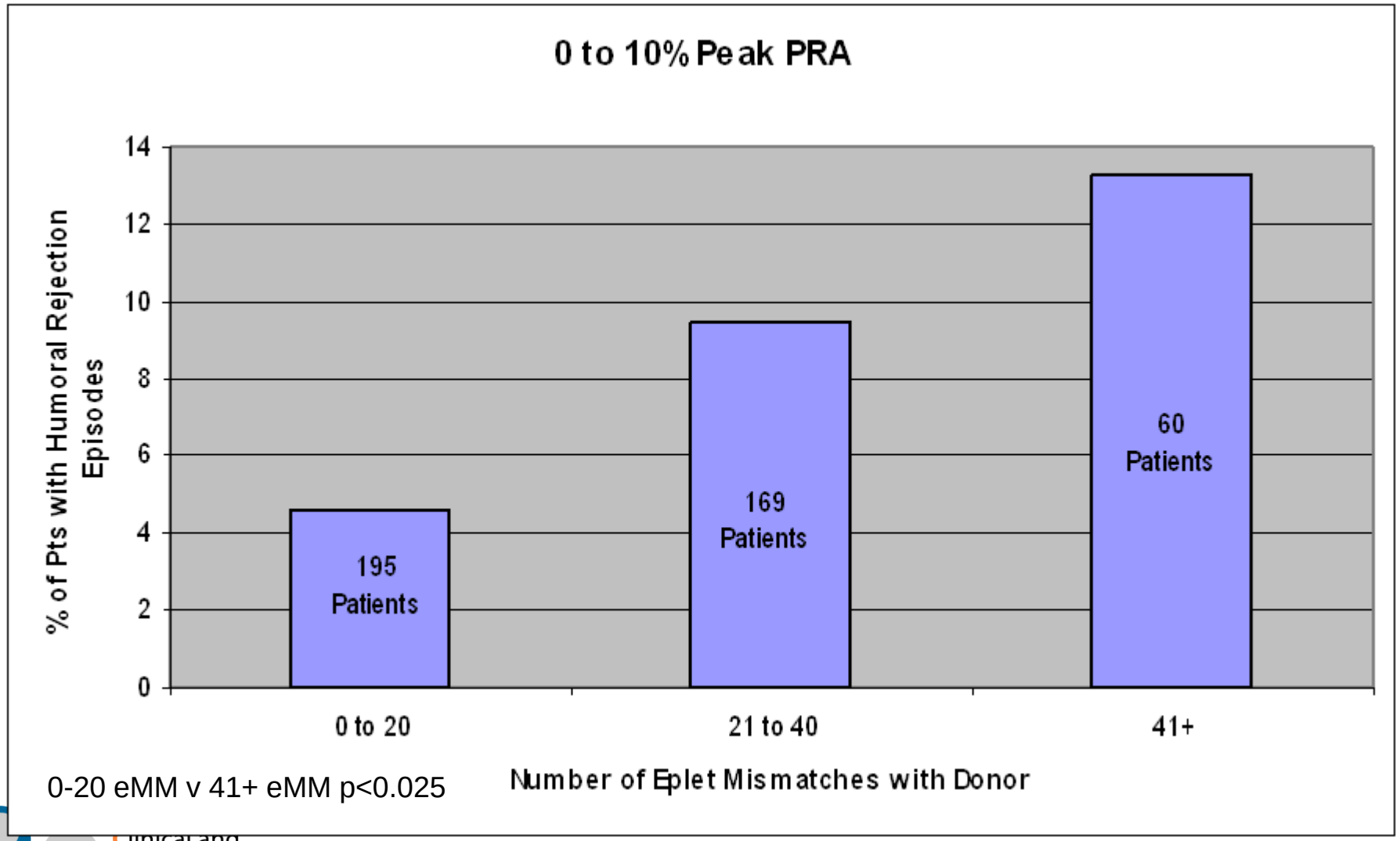
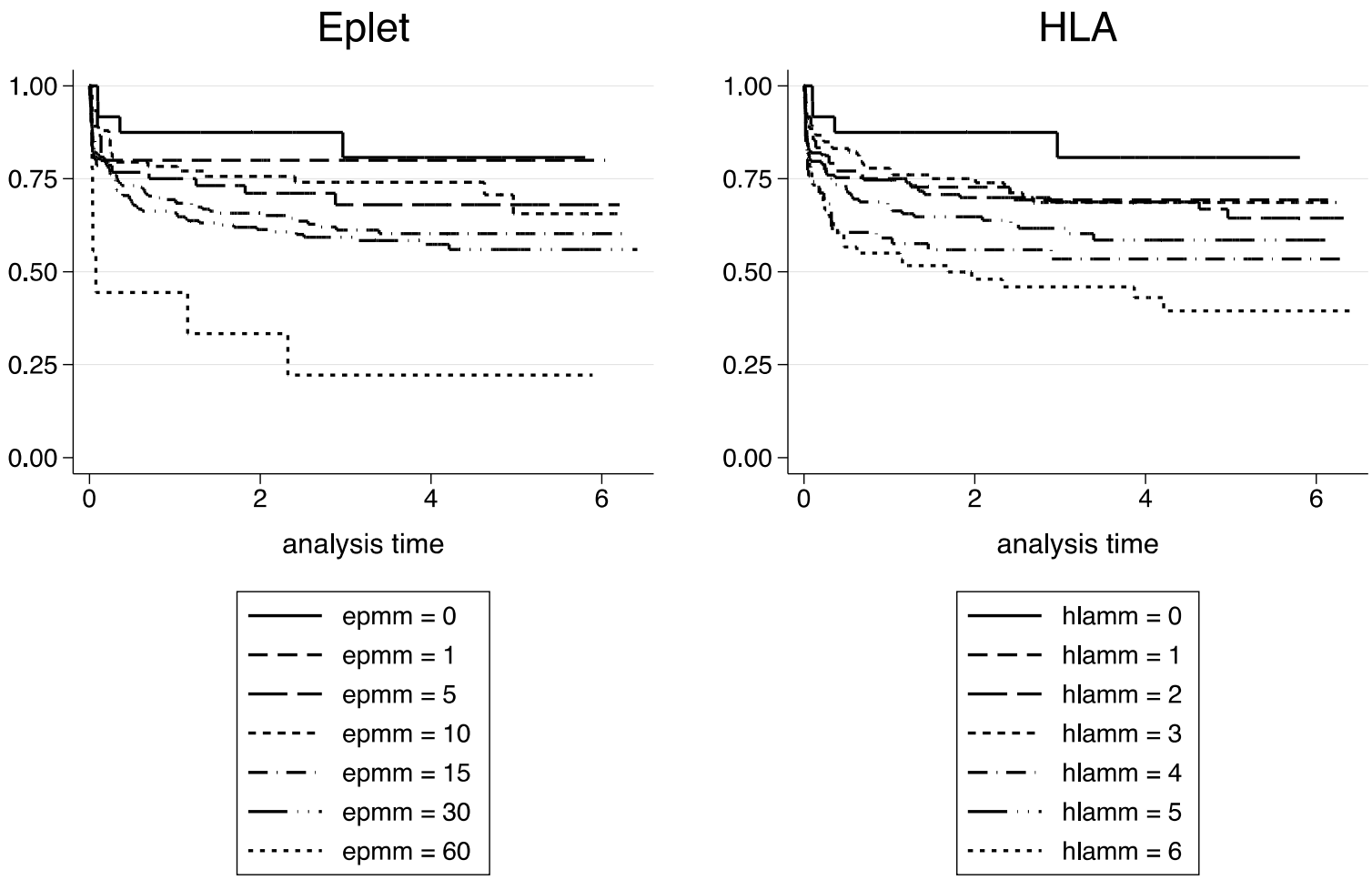
Humoral rejection in non sensitized patients and effect of Eplet mismatch



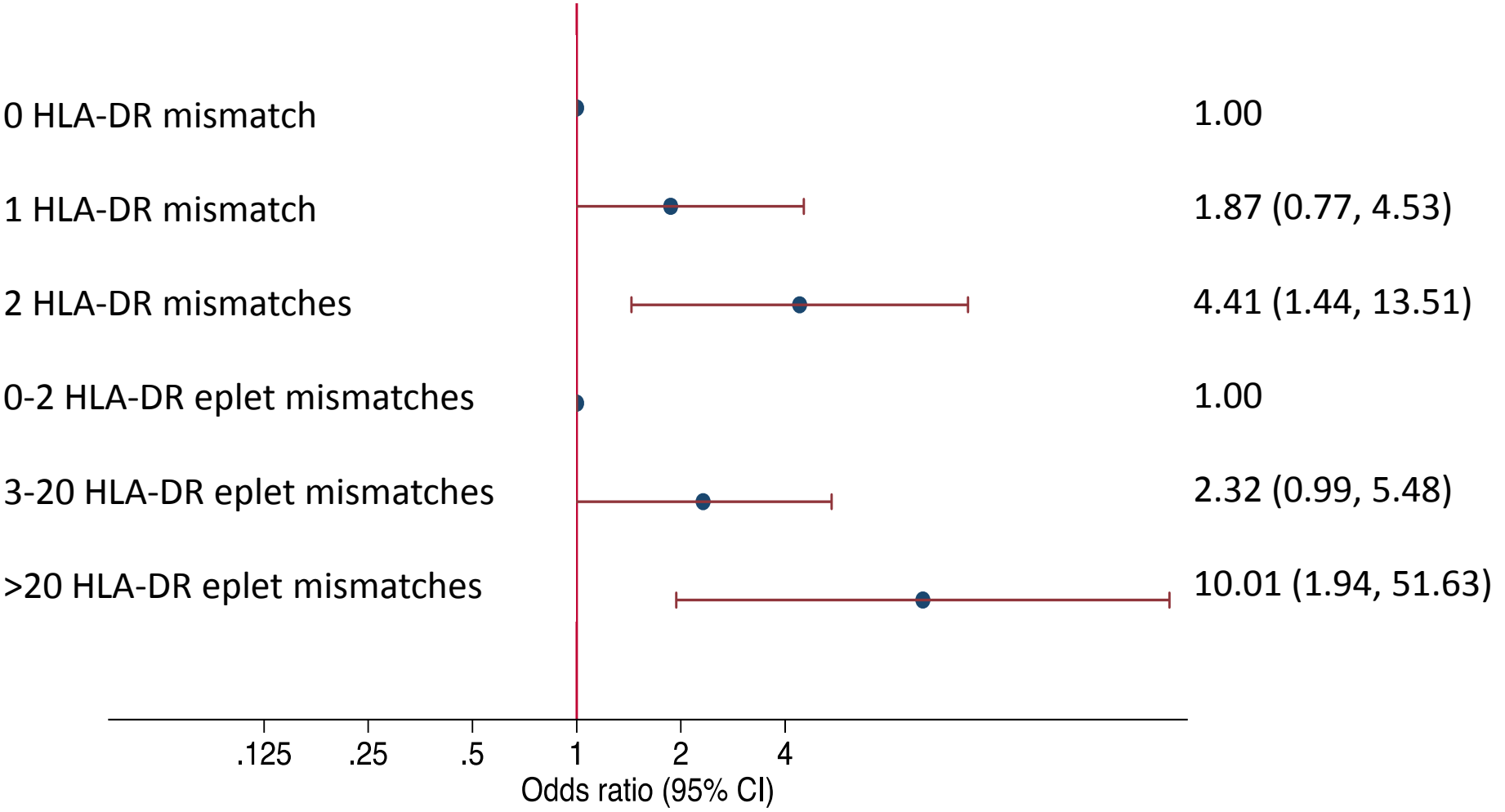
0-20 eMM v 41+ eMM p<0.025

Graft survival is shortened with high levels of HLA or Eplet mismatch



WESTERN AUSTRALIA TRANSPLANT COHORT 2003-2007 (N=258)

REJECTION



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(Courtesy Wai Lim)

Case 1 : Class I

							MM
R1	A24	A34	B13	B56	Cw1	Cw4	
D1	A1	A2	B8	B44	Cw5		22
D2	A11	A29	B7	B49	Cw3	Cw7	14
D3	A3	A26	B60	B75	Cw3		17
D4	A11	A66	B44	B39	Cw5		12

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Case 2: Class I

							MM
R2	A2	A34	B13	B56	Cw1	Cw4	
D1	A11	A25	B44	B57	Cw5	Cw6	22
D2	A1	A33	B57	B65	Cw6	Cw8	20

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Case 3: Class I

							MM
R3	A2	A34	B56	B13	Cw1	Cw4	
D1	A11	A25	B44	B57	Cw5	Cw6	22
D2	A1	A33	B65	B57	Cw6	Cw8	20
D3	A2-		B44-		Cw5		5
D4	A2-		B75-		Cw3		2

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Eplet matching issues

- Which locus to match class I or class II?
- Current patients should have Luminex based screening to determine sensitization status

Conclusions Immunological Assessment of Aboriginal Australians

- Restricted blood groups
- Increased Ig levels
- Restricted HLA class I
- Moderately diverse HLA class II
- Rethink allocation to possible structural based allocation?

“Much can be achieved if we do not care who gets the credit”

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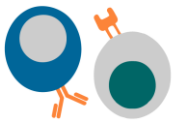
Next Steps

- Lloyd D'Orsogna communicated with Rene Duquesnoy to include AA type in next matchmaker
- Impact of Eplet matching to be modeled for SA/NT patients by Wai Lim and Germaine Wong
  - Assess impact on waiting times for other SA/NT recipients
  - Mechanism of how Eplet match would be included in allocation algorithm

Acknowledgements

- Greg Bennett
- Rhonda Holdsworth
- Amy Hahn
- Rob Carroll

- Stephen McDonald
- Matthew Jose
- Wai Lim



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