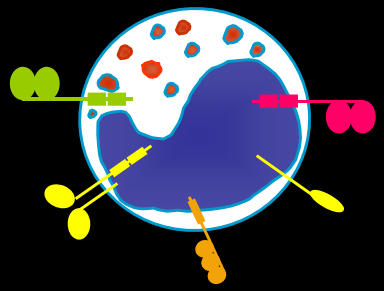

Population-Specific Evolution of Natural Killer Cell Diversity

‘Evolution’ Quotes 101

Nothing in Biology Makes Sense Except in the Light of Evolution

(Theodosius Dobzhansky, 1973)

'Evolution' Quotes 101

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It's a theory that's out there. It's got some holes in it.

(Rick Perry*, 2011)

*Candidate for USA President 2012-14

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...there's real consequences to evolution

(Rick Santorum*, 2009)

*Candidate for USA President 2012-14

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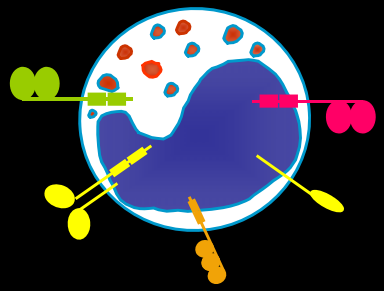
It's a theory that's out there. It's got some holes in it.
(Rick Perry*, 2011)

...there's real consequences to evolution
(Rick Santorum*, 2009)

From a scientific point of view we should lay out areas in which the evidence supports evolution and the areas where it does not.
(Rick Santorum, 2011)

*Candidate for USA President 2012-14



Population-Specific Evolution of Natural Killer Cell Diversity

NK cell Diversity; KIR and HLA

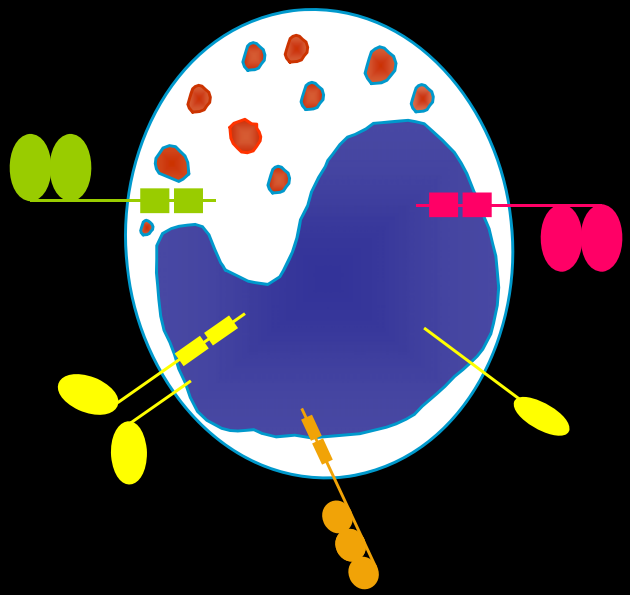
Maintenance of Diversity in Populations

Keeping the Balance

Extent of Diversity in Populations

(KIR in Ancient Humans)

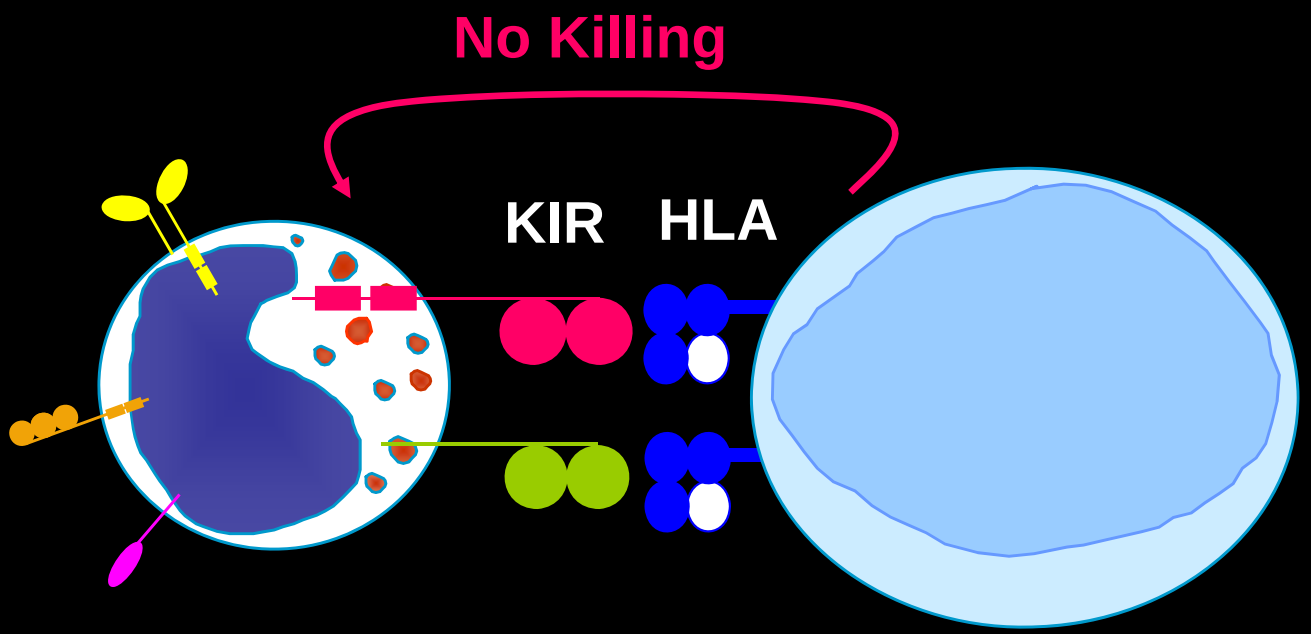
Natural Killer Cell Functions



Natural Killer Cell

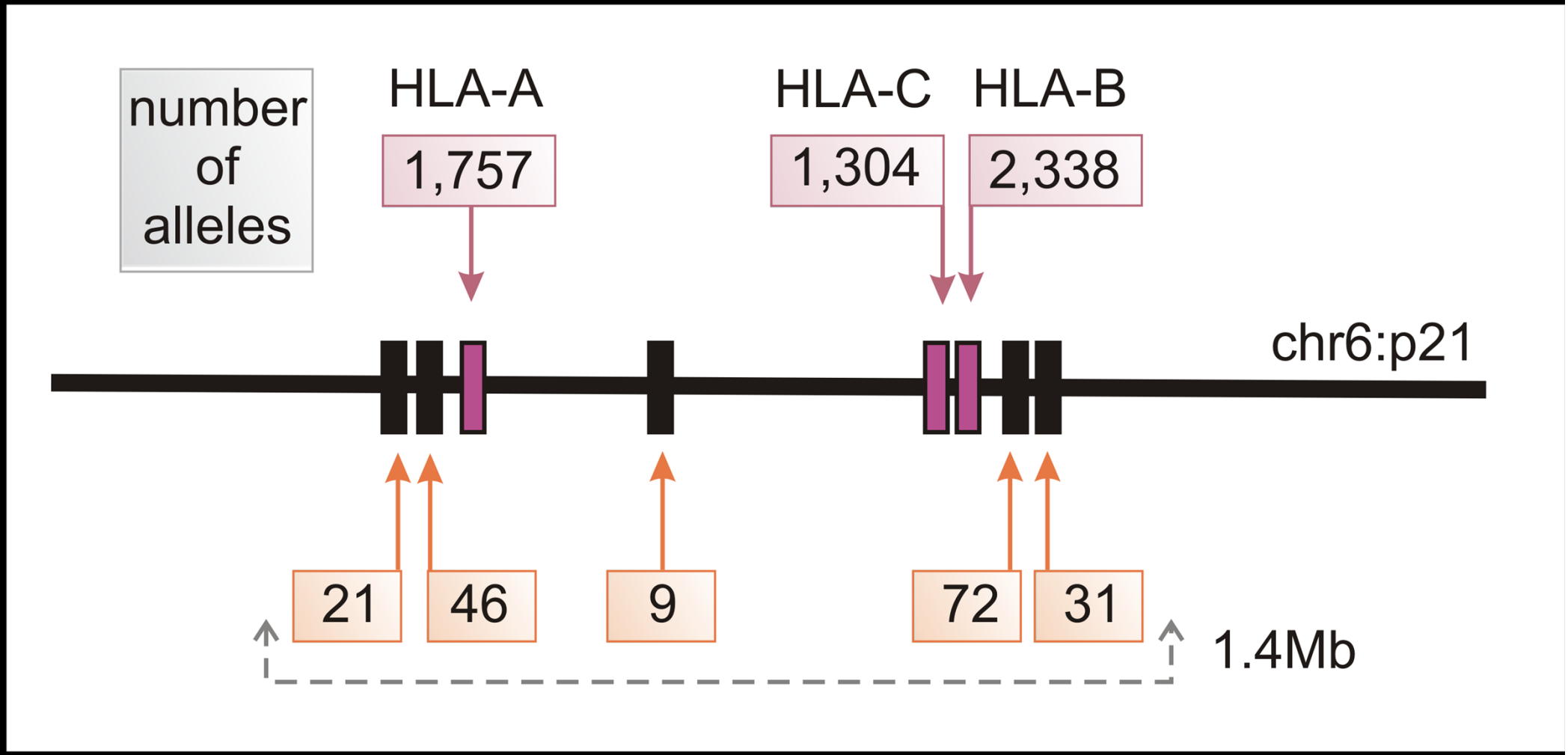
- **Infection control**
- **Reproduction**
- Tumour control
- Bridge Innate and Adaptive Immunity
- (Transplantation)

NK Cells controlled by receptors for HLA

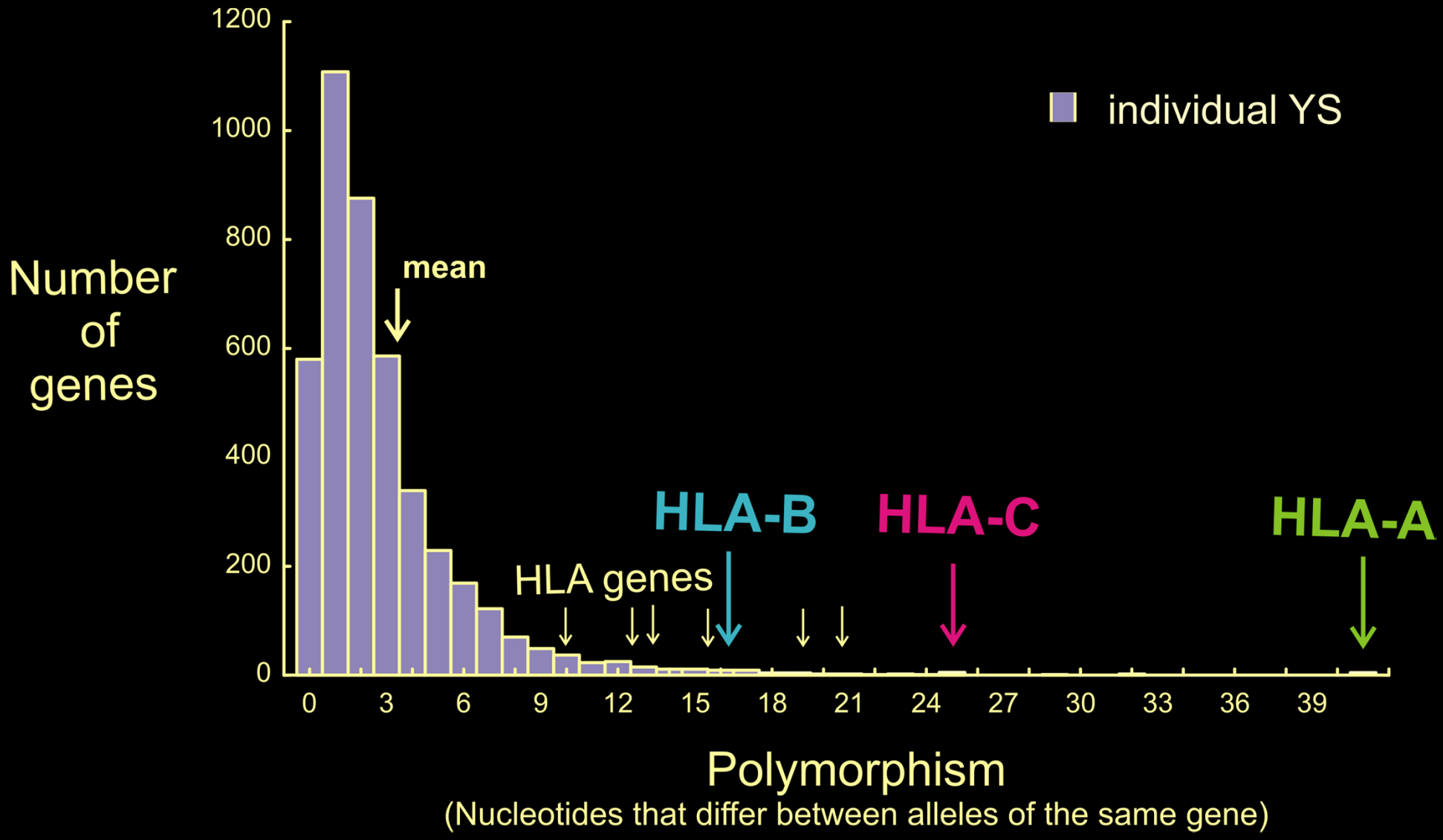


KIR = Killer cell Immunoglobulin-like Receptor
HLA = Human Leukocyte Antigen

HLA class I genes are highly Polymorphic (they have many alleles)



HLA are the Most Polymorphic Human Genes



Parham et al. 2011 *J. Imm*

KIR gene number is variable

KIR ‘A’ haplotypes

KIR ‘B’ haplotypes

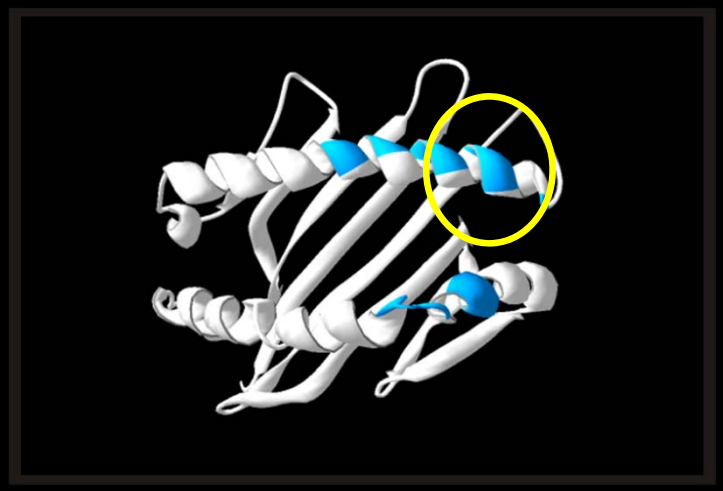
Framework Gene

Variable Gene

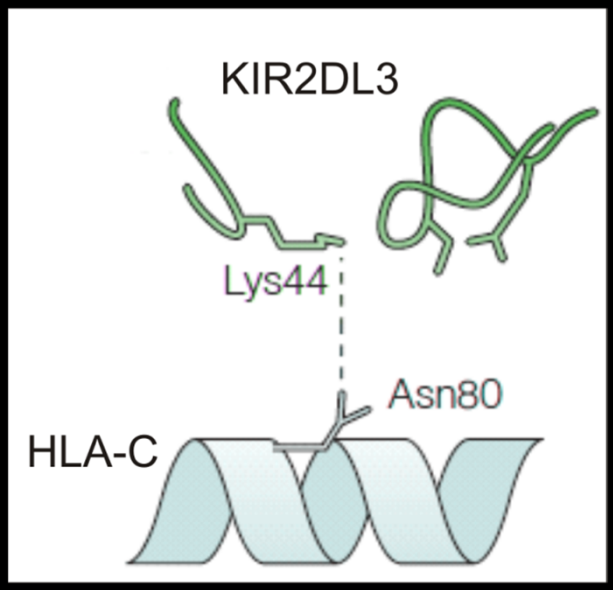
Haplotype = Unique array of genes inherited from one parent

Uhrberg et al. 1997 *Immunity*, Wilson et al. 2001 *PNAS*

KIR recognize specific epitopes of HLA molecules



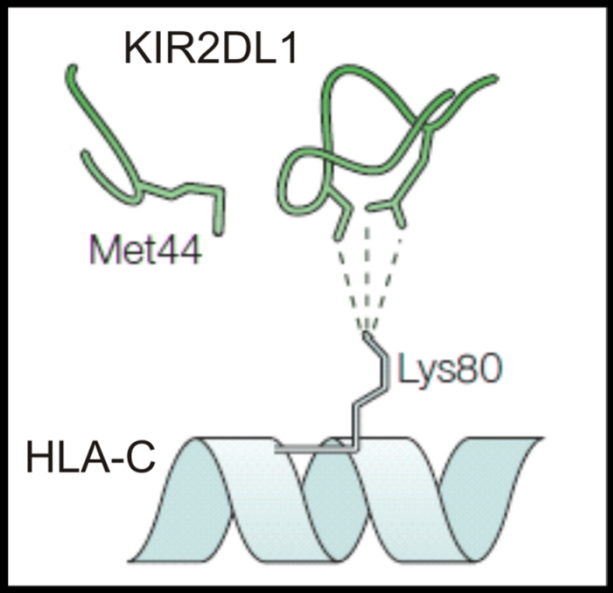
HLA-C



KIR2DL3

(K44)

HLA-C1



KIR2DL1

(M44)

HLA-C2

e.g. HLA-C dimorphism governs the specificity of binding to KIR2D

KIR 'A' Haplotypes; good for immunity, bad for reproduction

KIR2DL3

HLA-C1

Hepatitis C

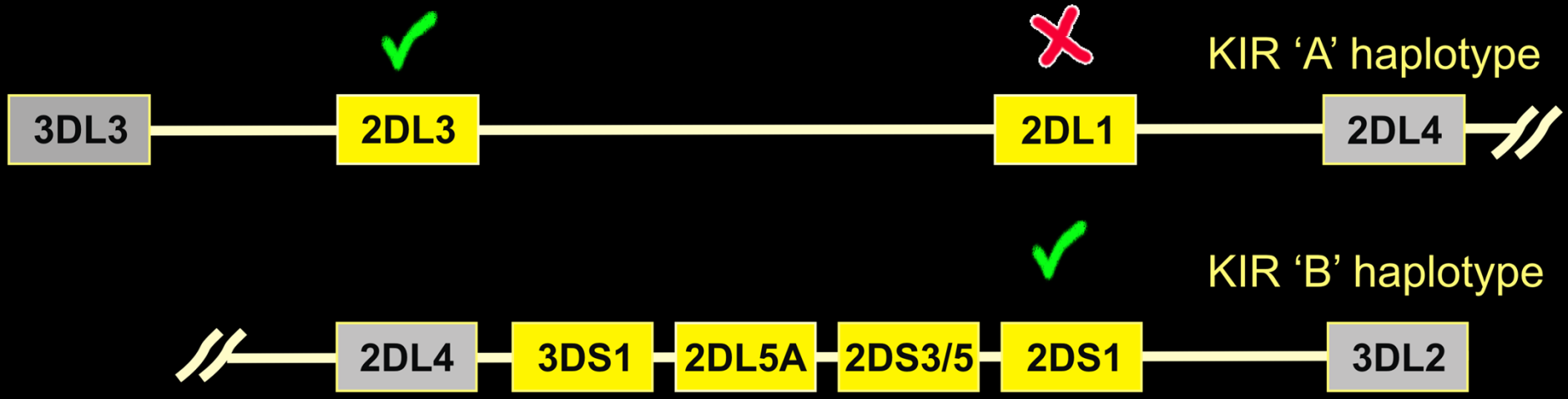
(Khakoo et al. 2004)

KIR2DL1

HLA-C2

Pre-eclampsia

(Hiby et al. 2004)



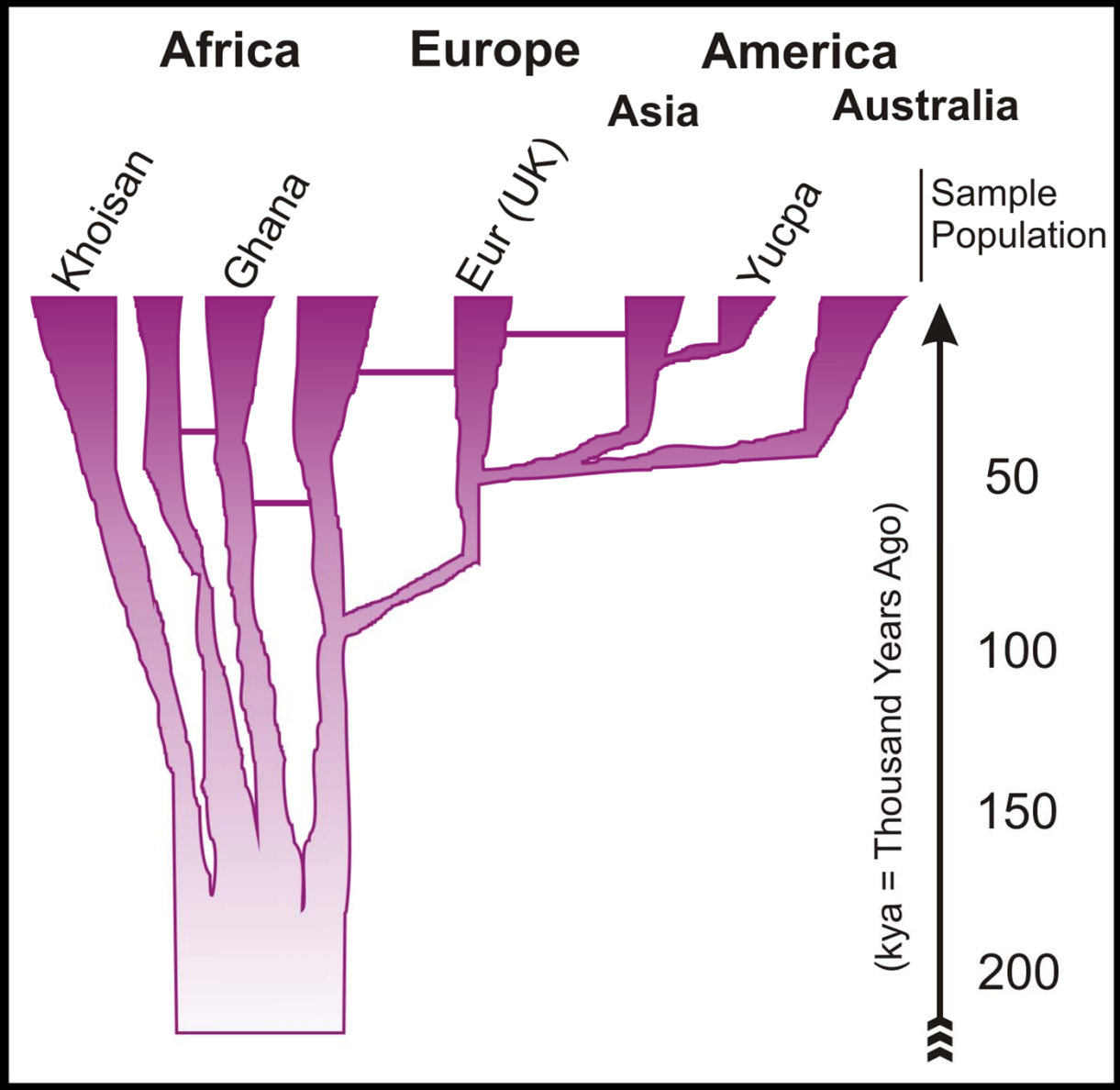
NK cell Diversity; KIR and HLA

Maintenance of Diversity in Populations

Keeping the Balance

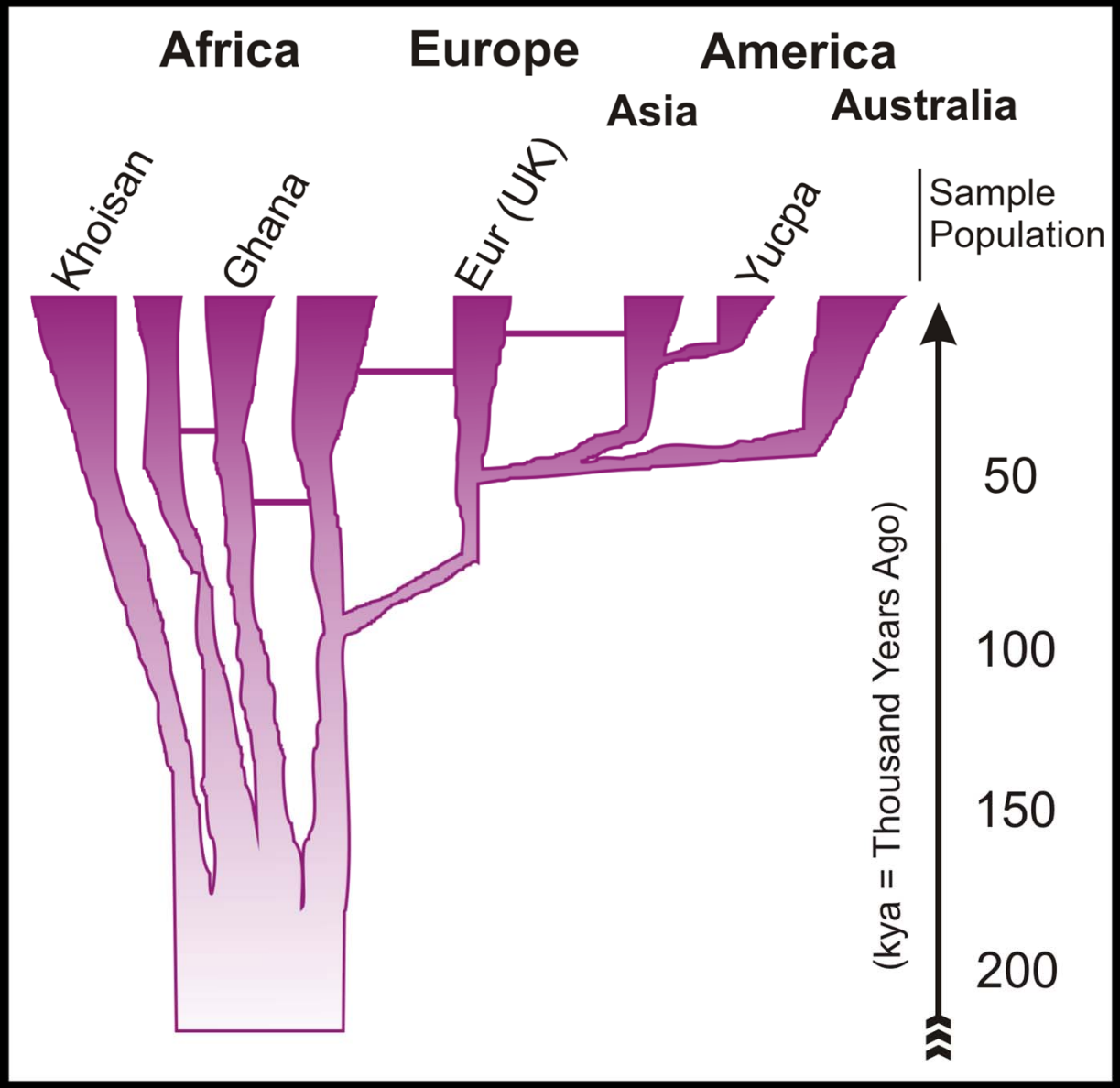
Extent of Diversity in Populations

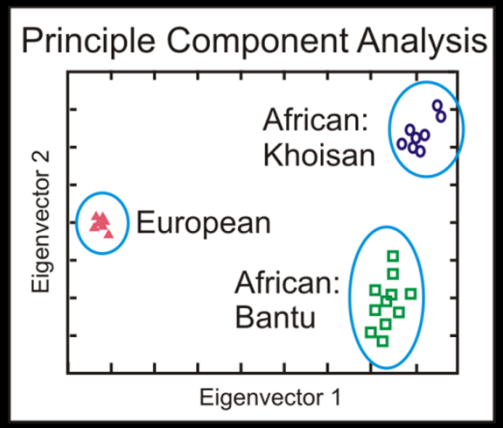
Modern Human History and Four Sample Populations



Adapted from Campbell & Tishkoff 2008 *Ann Rev Gen Hum Gen*

Modern Human History and Four Sample Populations





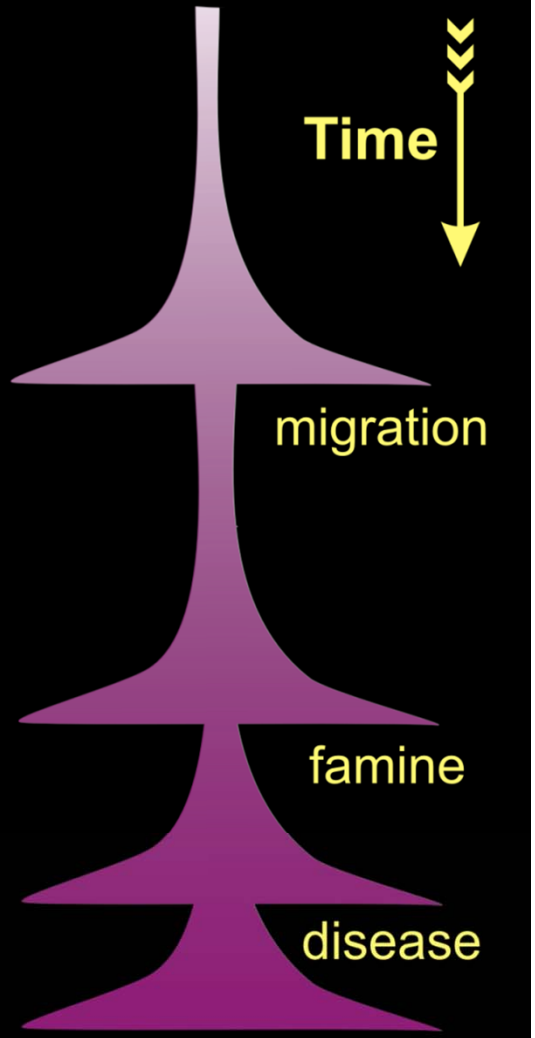
Henn et al. 2011

Adapted from Campbell & Tishkoff 2008 *Ann Rev Gen Hum Gen*

The Yucpa Amerindian Population has low Genetic Diversity due to Serial Bottlenecks

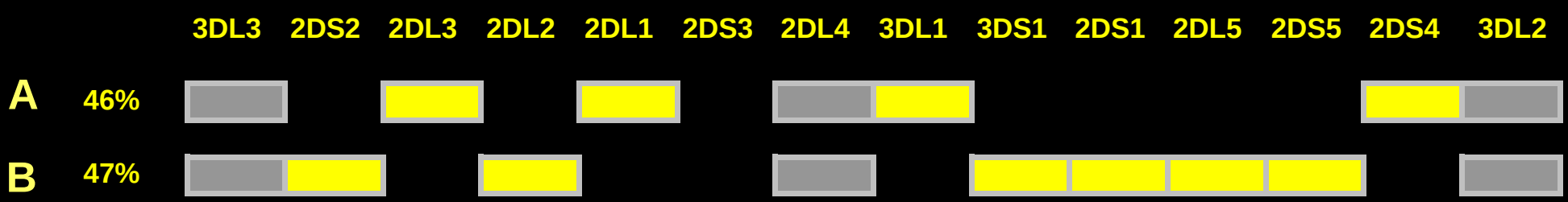
Yucpa

Venezuela



Two common and distinct *KIR* haplotypes in Yucpa

Infection



Reproduction

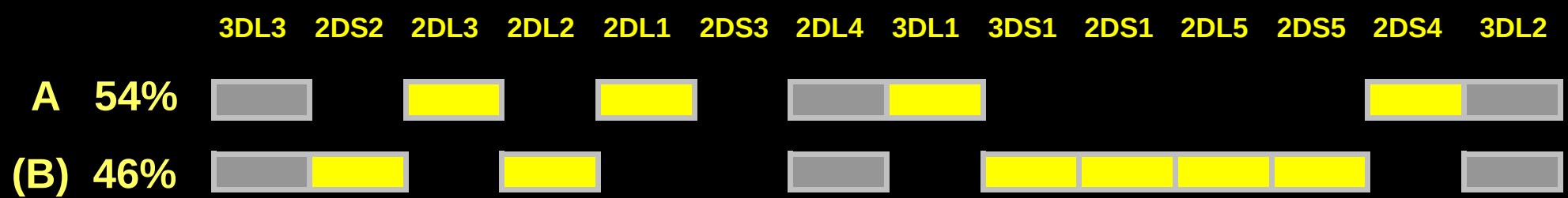
Gene present

Gene absent

Gendzekhadze et al. 2009 *PNAS*

Two common KIR haplotypes in Europeans

Infection

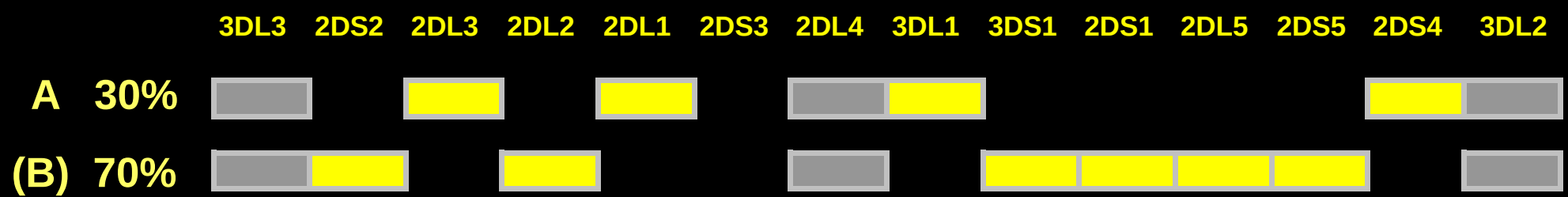


Reproduction

Norman et al. 2004
Immunogenetics

Two common KIR haplotypes in Indians

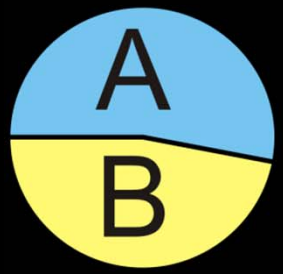
Infection

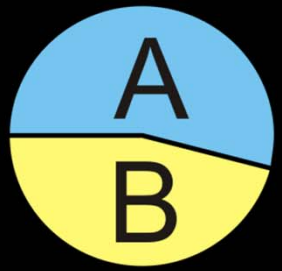


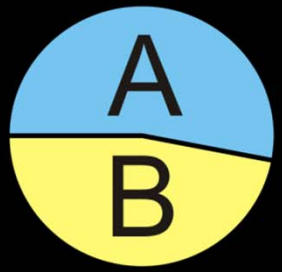
Reproduction

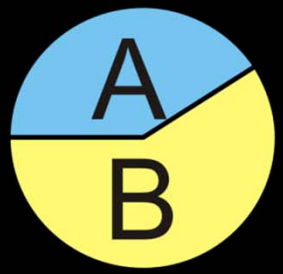
Rajalingam et al. 2002
J. Immunol

A and B KIR haplotypes in balance worldwide









Yucpa

European

Ghanaian

Khoisan

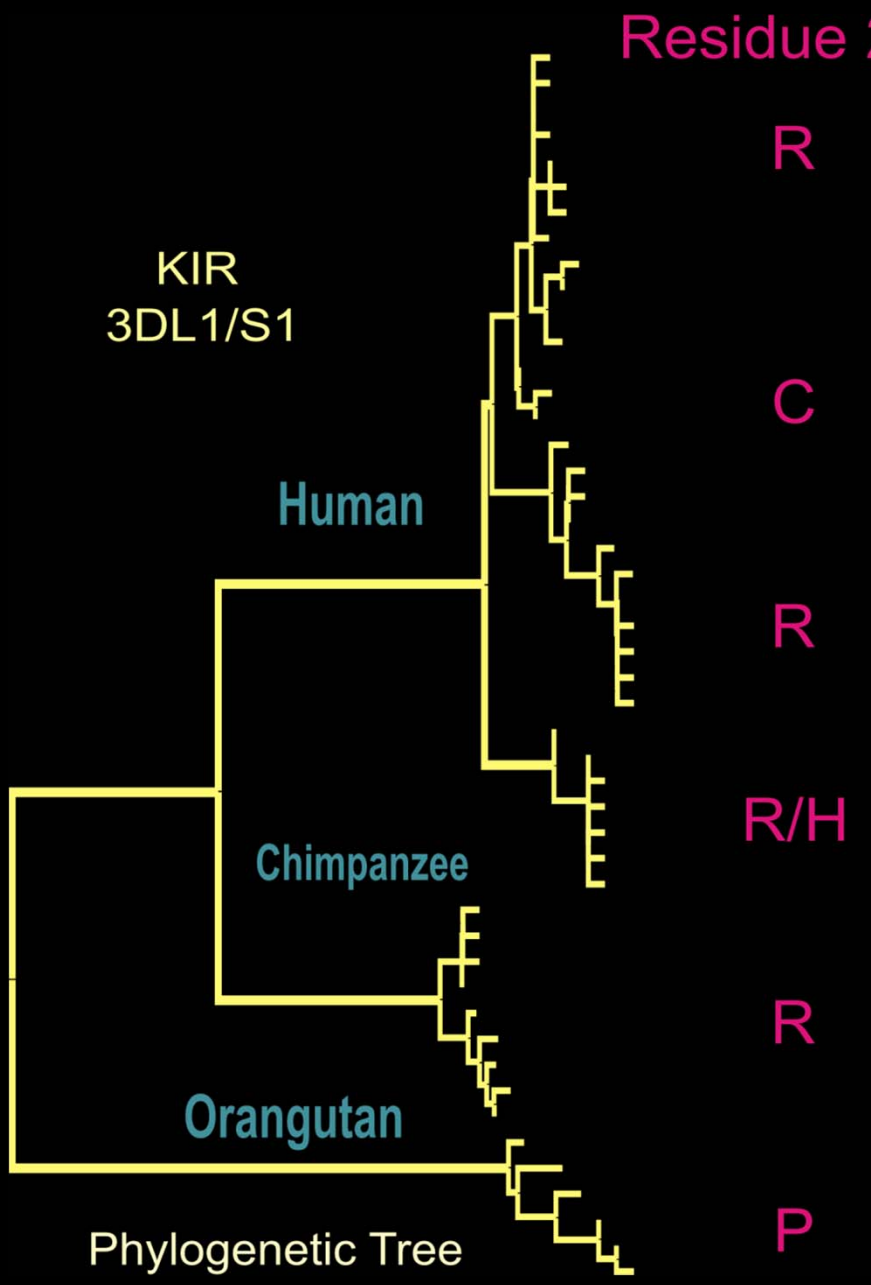
Diversity of KIR and HLA

Maintenance of Diversity in Populations

Keeping the Balance

Extent of Diversity in Populations

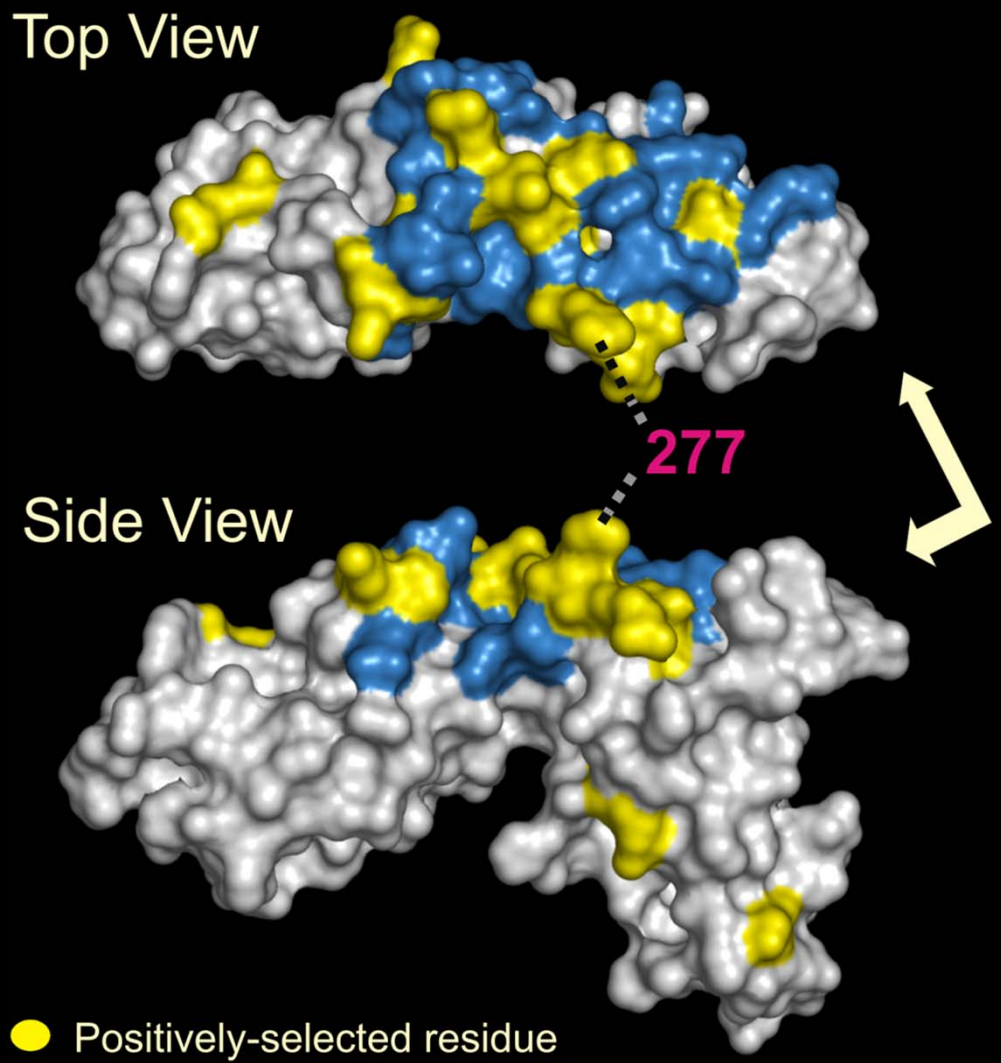
Identifying Specific Amino Acids under Natural Selection



Amino Acid Residue	Selection Probability Value
5	**0.95**
20	0.85
31	0.80
32	**0.96**
51	**0.96**
118	**0.97**
136	0.82
138	0.77
141	0.77
145	0.67
165	0.87
166	0.79
182	0.65
199	**0.97**
218	0.70
227	0.70
243	0.81
277	**0.97** *
278	0.68
282	**0.95**
283	**0.97**

Selection analysis

Positive selection focused to ligand binding-site of KIR

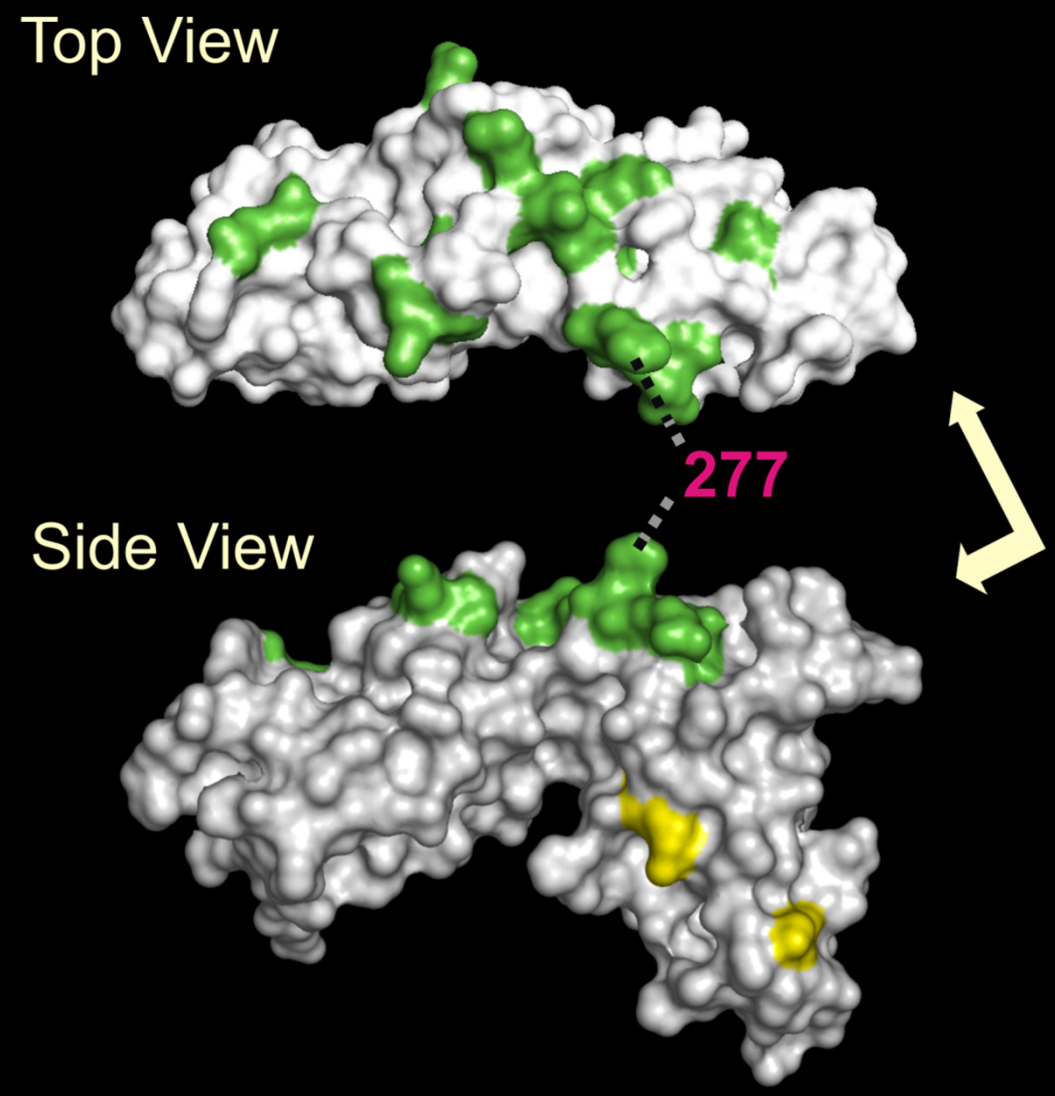


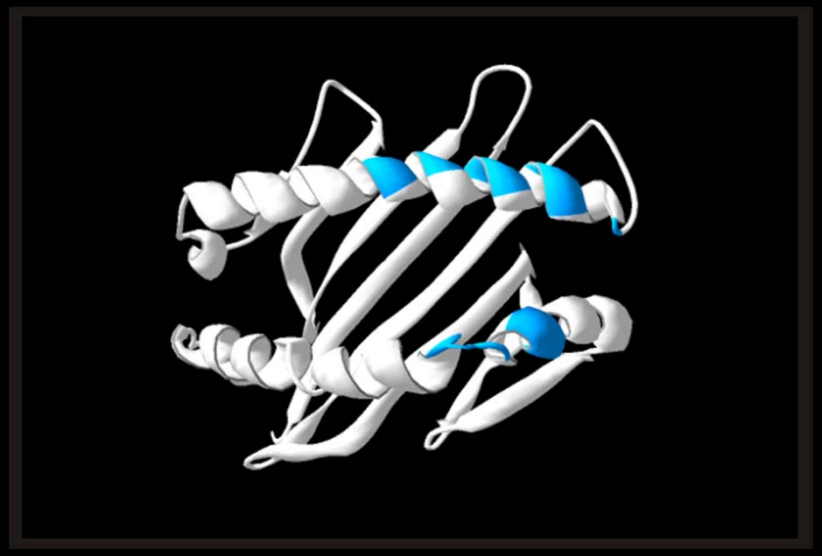
KIR

HLA Ligand

Norman et al. 2007 *Nat Gen*

Positive selection focused to ligand binding-site of KIR





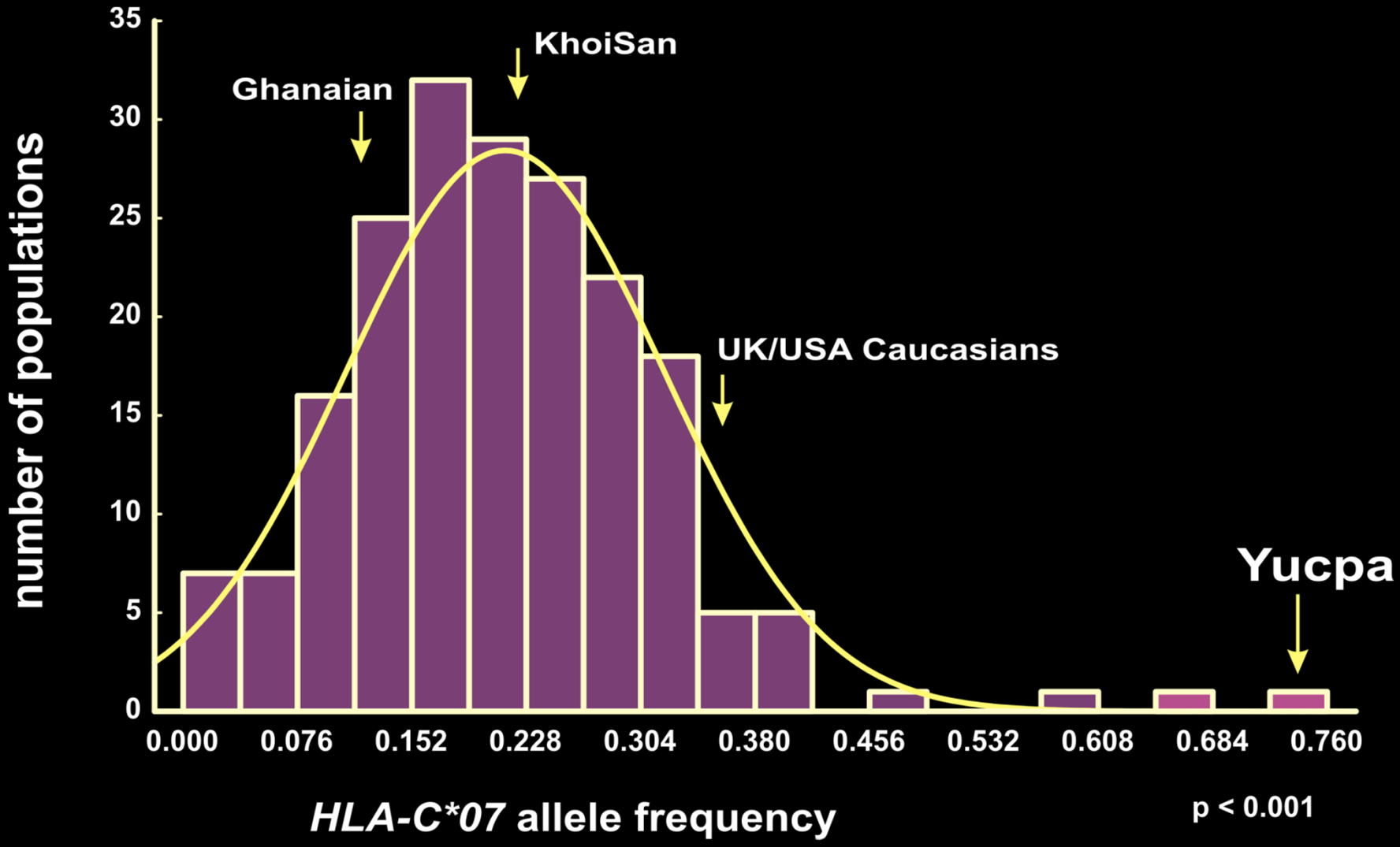
HLA Ligand

Positively-selected binding-site residue

KIR

Norman et al. 2007 *Nat Gen*

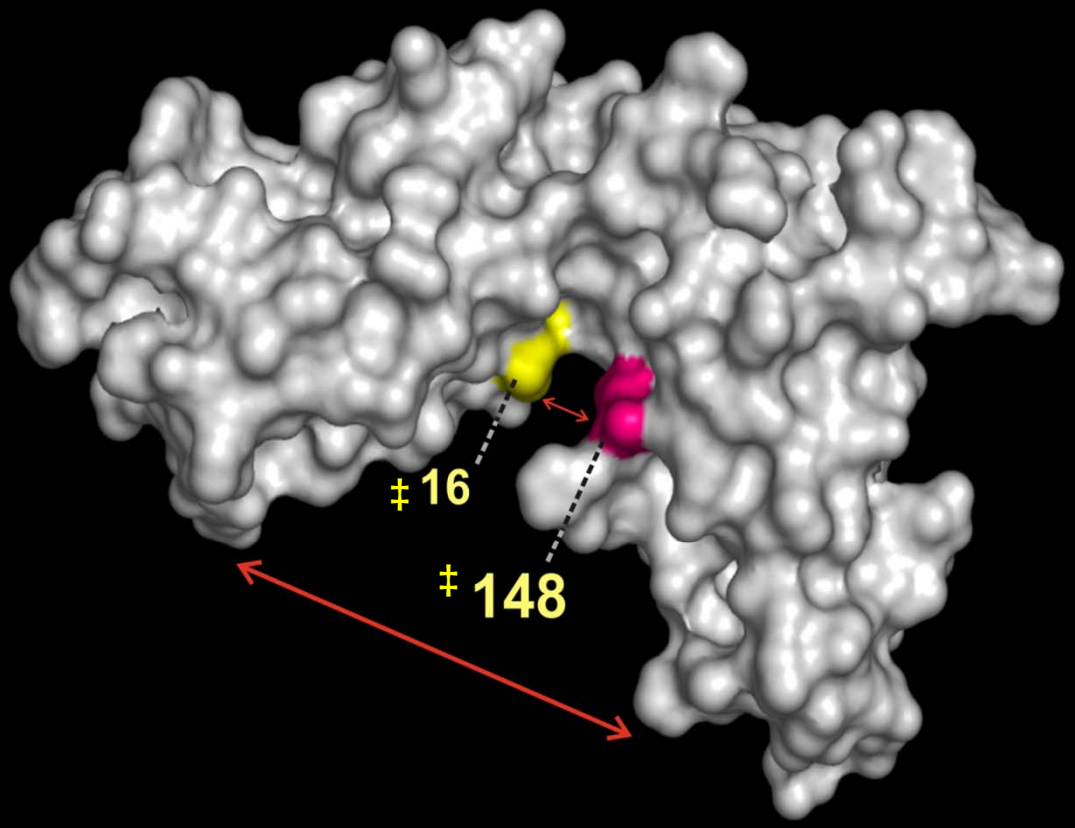
An unusually high frequency of HLA-C*07 in the Yucpa



Gendzekhadze et al. 2009 *PNAS*

Two *KIR2DL3* alleles are Unique to the Yucpa

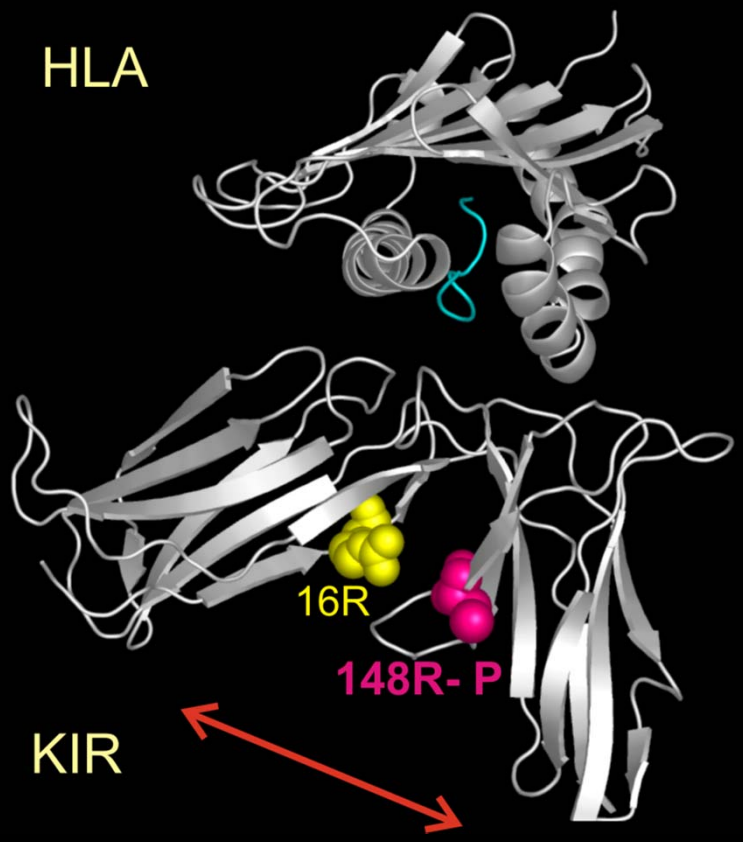
KIR2DL2/3	Frequency (%)	Amino Acid Position ‡16	124	‡148
*2DL2*003*	44.9	**R**	V	**C**
*2DL3*001*	8.2	P	V	R
2DL3*008N	**7.4**	**P**	**Ter**	
2DL3*009	**34.4**	**P**	**V**	**P**



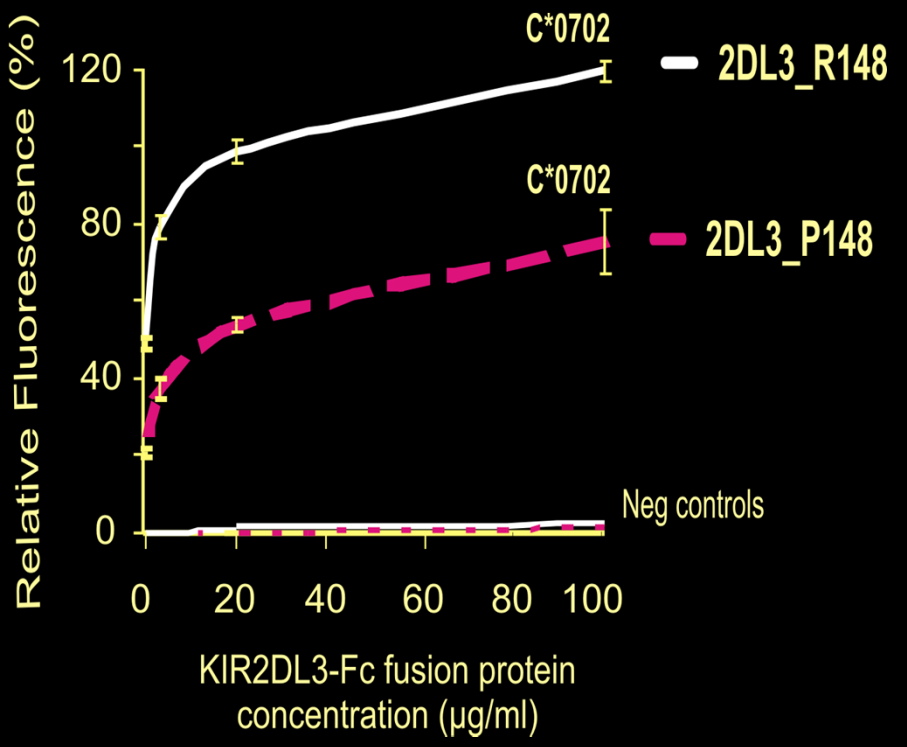
‡ Positively-selected Site

Moesta et al. 2008 *J. Imm*,
Abi-Rached et al. 2010 *Plos Gen*

Yucpa 2DL3*009 has reduced HLA-C*07 binding



KIR/HLA interaction



Cell-free binding Assay

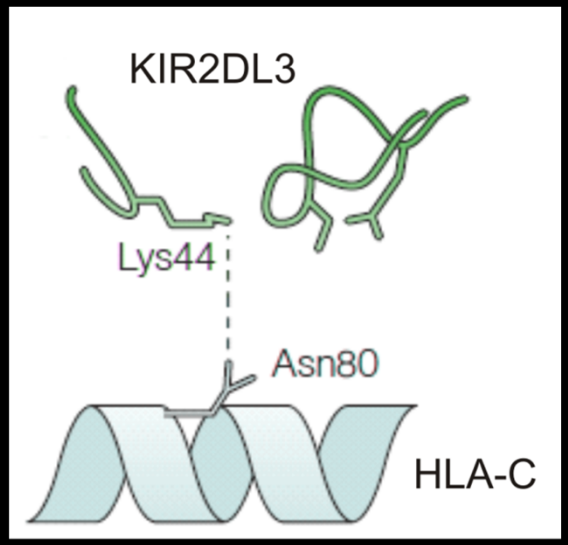
Gendzekhadze et al. 2009 *PNAS*


Khoisan
Africa

KIR2DL1-K44 is an allele unique to Khoisan

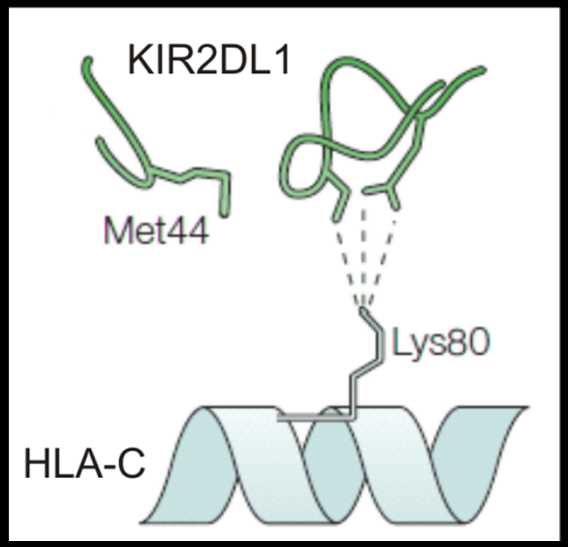
KIR2DL2
(K44)

HLA-C1

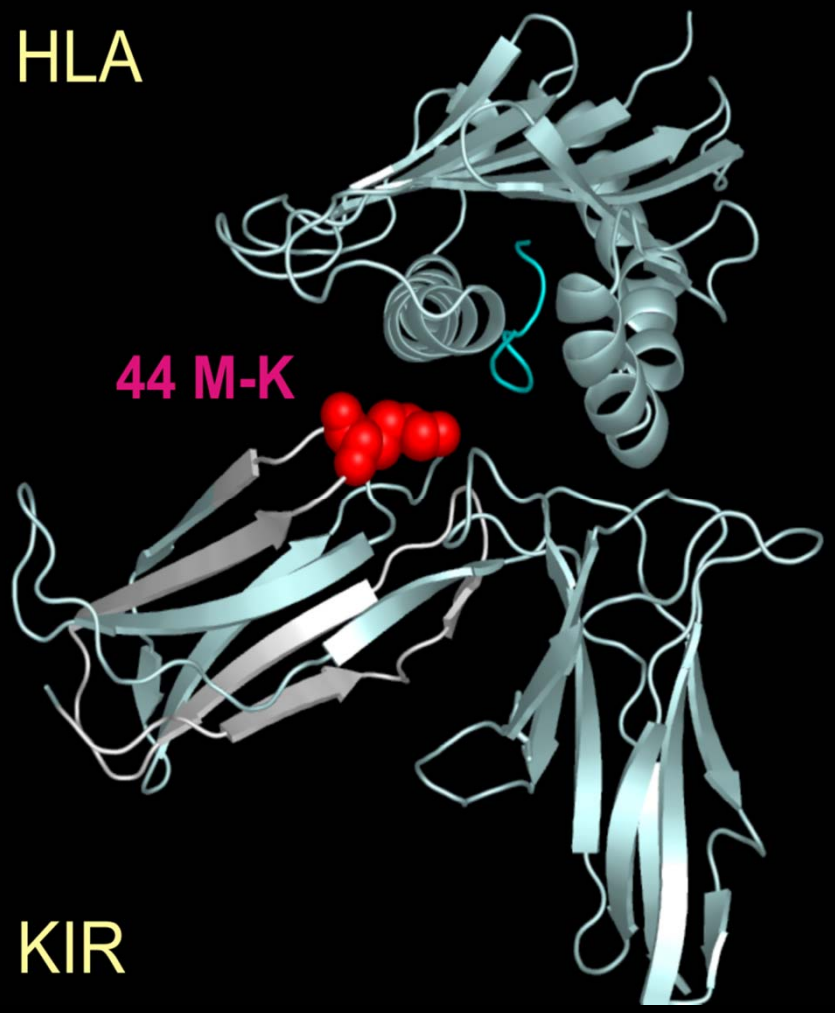


KIR2DL1
(M44)

HLA-C2

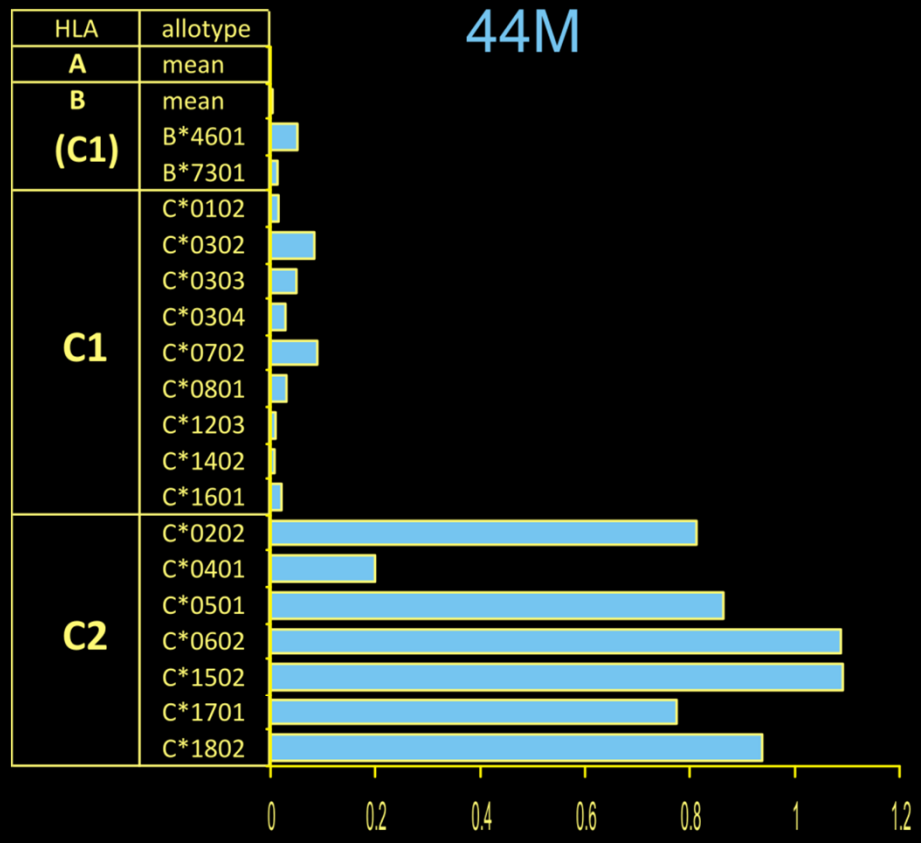


HLA-C dimorphism governs the specificity of binding to KIR2D

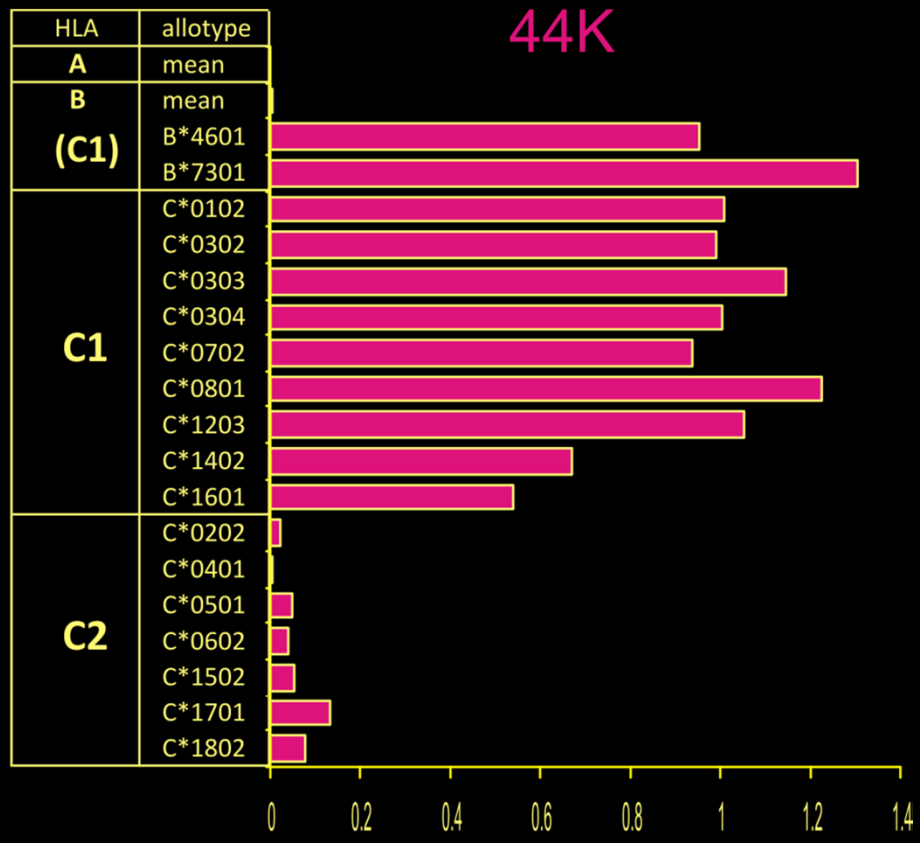


2DL1-K44

2DL1*022, Unique to Khoisan, has Switched HLA Binding Specificity



2DL1*003



2DL1*022

Diversity of KIR and HLA

Maintenance of Diversity in Populations

Keeping the Balance

Extent of Diversity in Populations

Understanding the extent of KIR/HLA diversity

Time

Constant

Recent
Expansion

Very High *KIR* and *HLA* Combinatorial Diversity in Ghana

1. Per-population

	KIR Alleles	
N	**Total**	**Novel**
186	**130**	**43**

	Haplotypes	Heterozygosity	
KIR	**204**	**0.99**	} 1
HLA Class I	**188**	**0.99**	}

Every Ghanaian has a unique immune system

Very High *KIR* and *HLA* Combinatorial Diversity

2. Per-individual

KIR Type	3DL3	2DS2	2DL3	2DL2	2DL1	2DS3	2DL4	3DL1	3DS1	2DL5	2DS5	2DS1	2DS4	3DL2	
			*001		*003		*005	*001					*001	*013	A
				*006			*005		*013			*002		*007	B

HLA Type

A*03:01 B*42:01 C*17:01 G*001

A*23:01 B*52:01 C*16:01 G*001

Compound Genotype: KIR and HLA

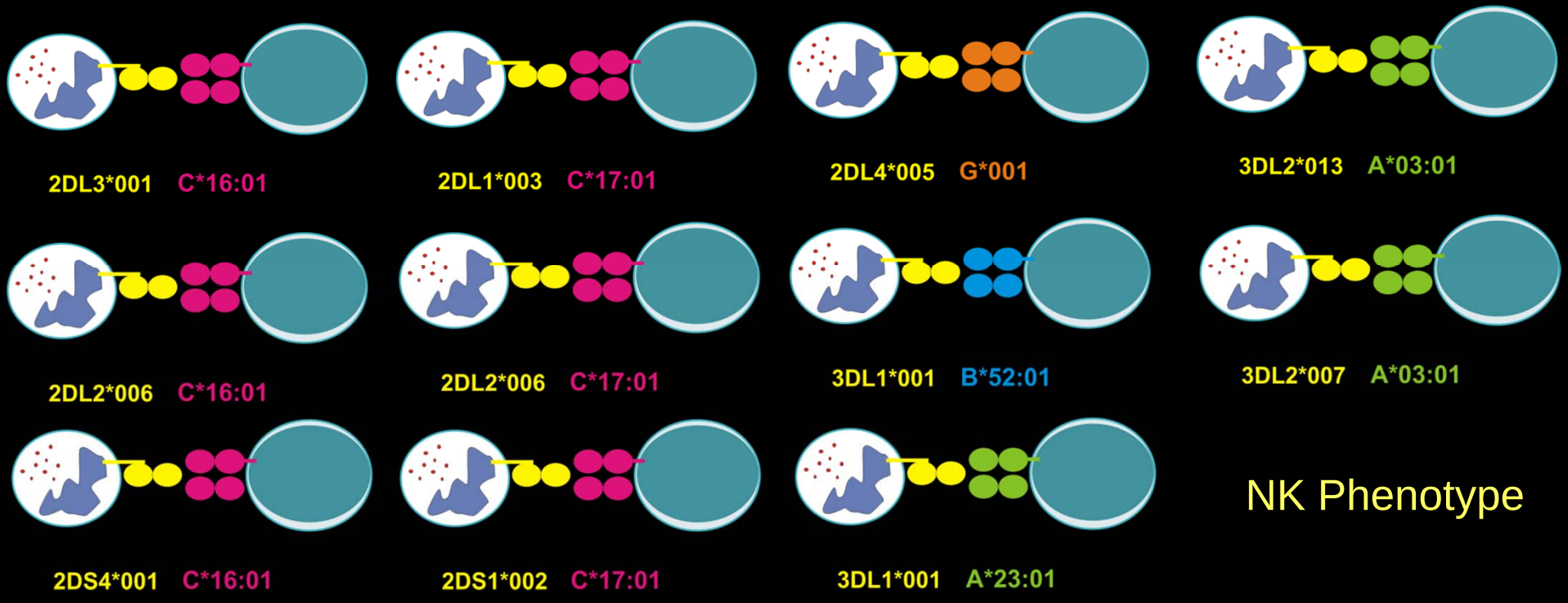
Individualized NK Repertoire

KIR Type	3DL3	2DS2	2DL3	2DL2	2DL1	2DS3	2DL4	3DL1	3DS1	2DL5	2DS5	2DS1	2DS4	3DL2	
			*001		*003		*005	*001					*001	*013	A
				*006			*005		*013			*002		*007	B

HLA Type

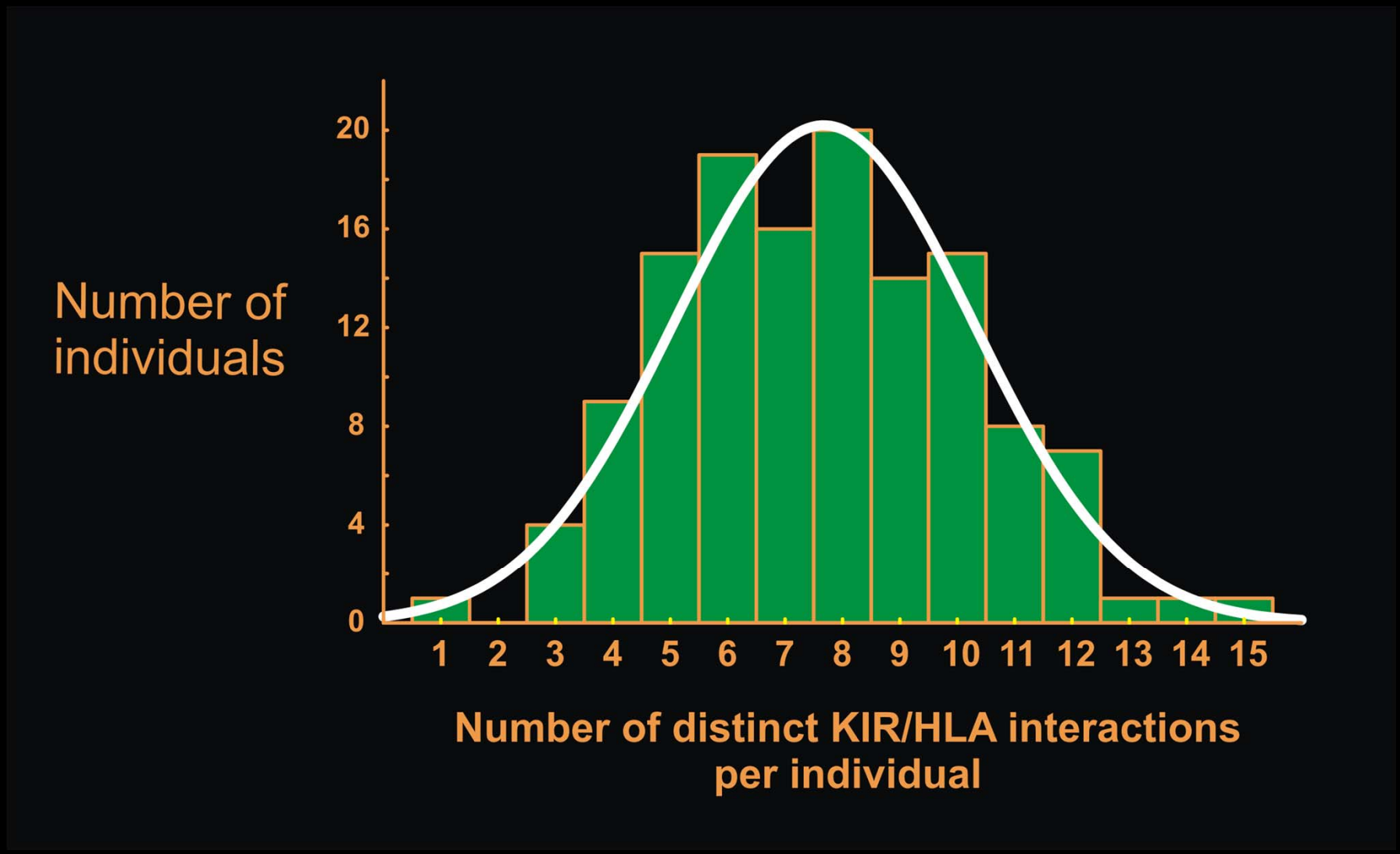
A*03:01 B*42:01 C*17:01 G*001

A*23:01 B*52:01 C*16:01 G*001



NK Phenotype

NK Repertoire Diversity as a Quantitative Trait



Conclusions

Diversity of KIR and HLA

- Both are highly variable

Maintenance of Diversity in Populations

- A and B haplotypes (infection vs. reproduction)

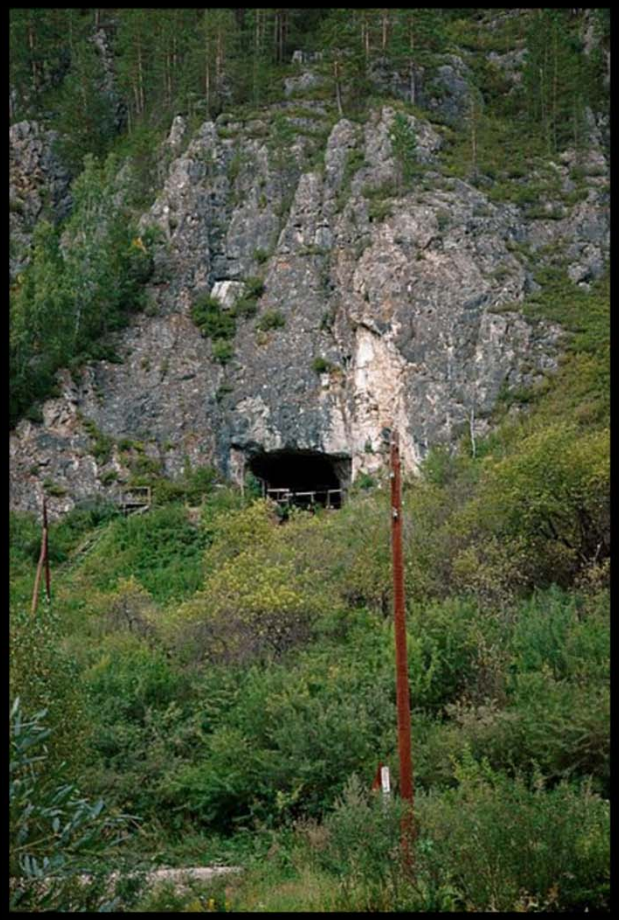
Keeping the balance

- Fine-tuning by single mutations

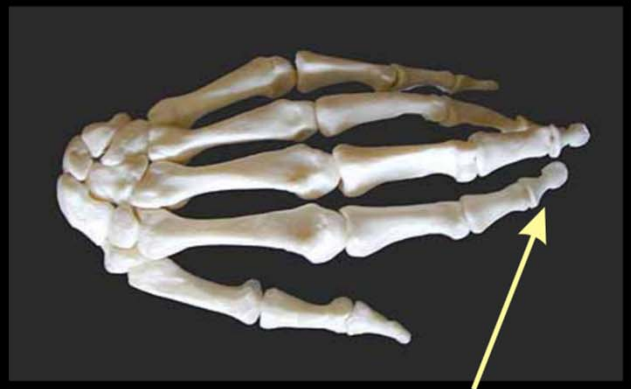
Sub-Saharan African populations, immune identity

- Normal phenotype distribution of NK interactions

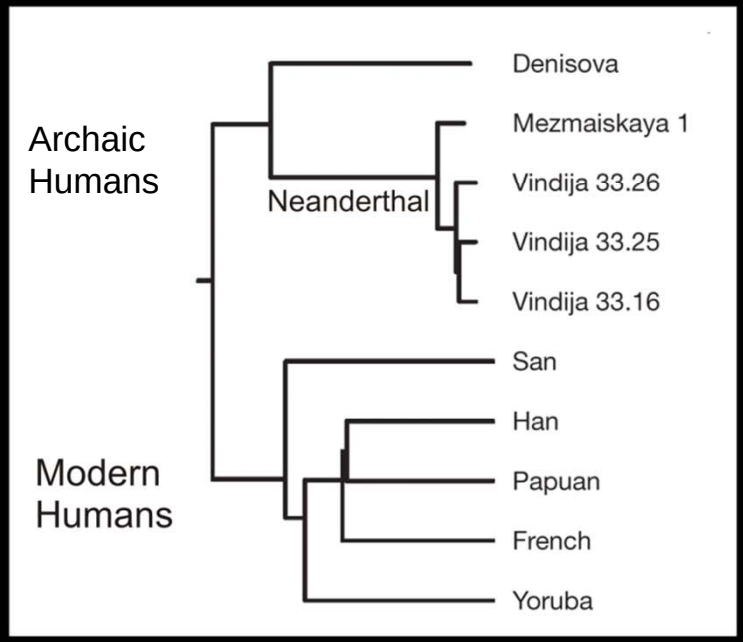
Genetic history of an archaic hominin group from Denisova Cave in Siberia



Denisova, Neanderthal and Modern Humans all co-existed

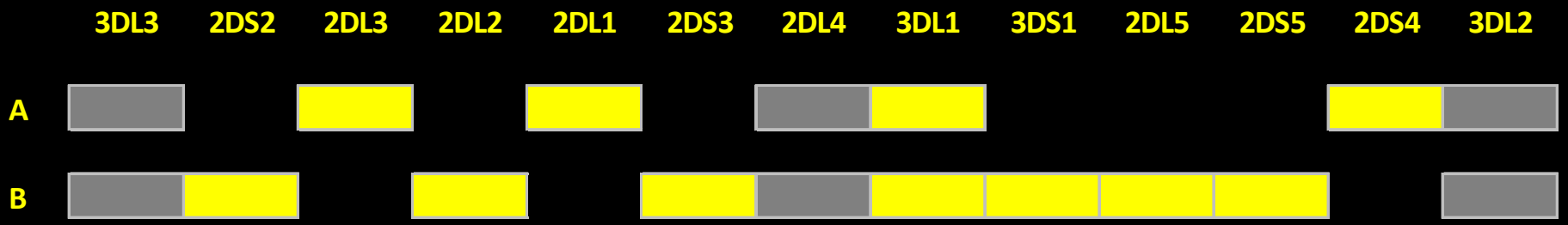


Ancient DNA from preserved finger bone

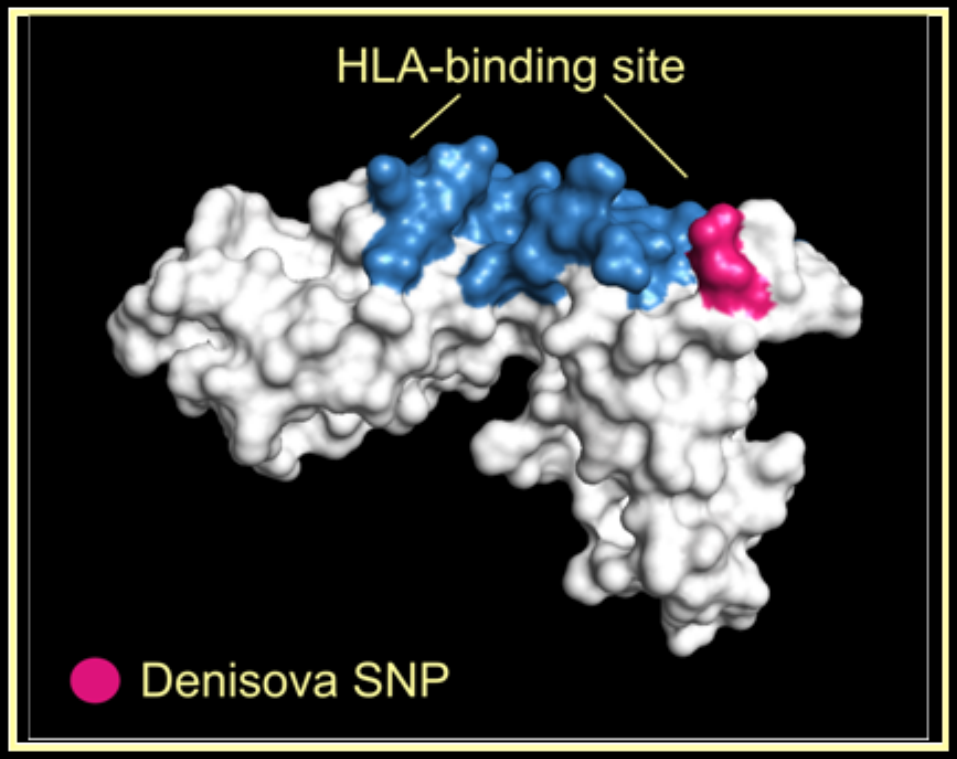


Reich *et al*. Nature 2010

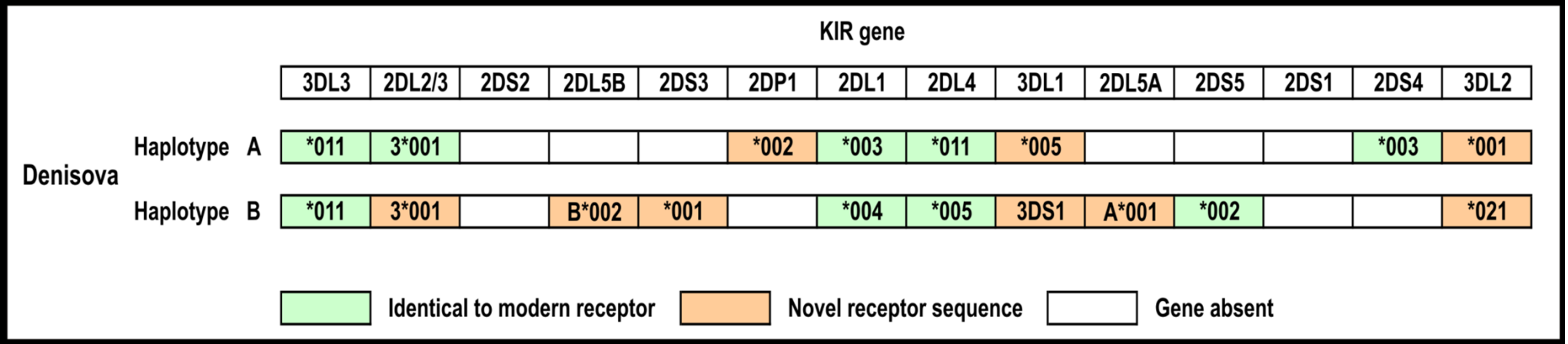
Denisova has *KIR A* and *B* haplotypes



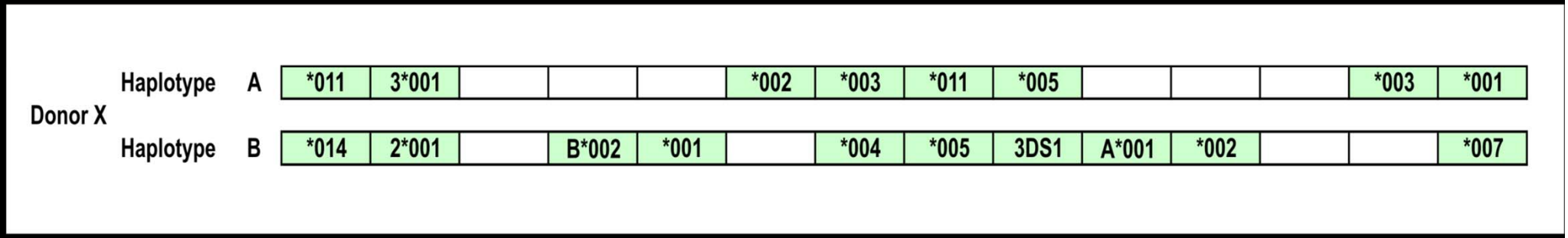
Denisova KIR3DL1/S1 may have unique specificity



Dennisova Vs. modern human KIR genotype



Full allele-level KIR genotype of Denisova



Full allele-level KIR genotype of a Modern Human

Conclusions ii
(Ancient Humans)

Diversity of KIR and HLA

Both are highly variable

Maintenance of Diversity in Populations

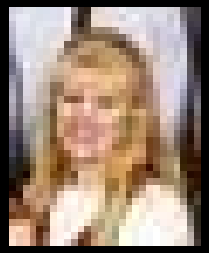
A and B haplotypes (infection vs. reproduction)

Keeping the balance

Fine-tuning by single mutations

Acknowledgements

- **Peter Parham**
- Ketevan Gendzekhadze
- Lisbeth Guethlein
- Laurent Abi-Rached



Ana Older Aguilar

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Acknowledgements

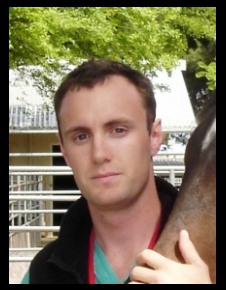
- **Peter Parham**

- Ketevan Gendzekhadze

- Lisbeth Guethlein

- Laurent Abi-Rached

Ana Older Aguilar



Hugo Hilton

Neda Nemat-Gorgani

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Acknowledgements

Stanford Genome Technology Centre
Mostafa Ronaghi
Baback Gharizadeh

Dept Genetics
Brenna Henn

Zulay Layrisse
Mark Leppert
Kwandwo Koram

All of the DNA donors