The Extraordinary Immunogenetics of Natural Killer (NK) Cell Receptors and Major Histocompatibility Complex (MHC) Class I Ligands

February 24th 2012

Peter Parham

Departments of Structural Biology and
Microbiology & Immunology, Stanford University

Evolutionary Origins of Compartmentalized Cells

International Center for Theoretical Sciences
National Center for Biological Sciences,
Bangalore, India

The Extraordinary Immunogenetics of Natural Killer (NK) Cell Receptors and Major Histocompatibility Complex (MHC) Class I Ligands

Laurent Abi-Rached
Paul Norman
Lisbeth Guethlein
Ketty Genzekhaze
Achim Moesta
Ana Older Aguilar
Hugo Hilton

Richard Green, University of California, Santa Cruz

Ashley Moffett, University of Cambridge

Bone-marrow transplant donor registries worldwide

The Extraordinary Immunogenetics of Natural Killer (NK) Cell Receptors and Major Histocompatibility Complex (MHC) Class I Ligands

[1] Conserved and variable natural killer cell rceptors that recognize MHC class I molecules

[2] Co-evolution of variable NK cell receptors with MHC class I

[3] Human-specific evolution of variable NK cell receptors.

The Extraordinary Immunogenetics of Natural Killer (NK) Cell Receptors and Major Histocompatibility Complex (MHC) Class I Ligands

[1] Conserved and variable natural killer cell rceptors that recognize MHC class I molecules.

The Major Histocompatibility Complex (MHC): Discovery and Clinical Relevance

The Major Histocompatibility Complex (MHC): Discovery and Clinical Relevance

[1] The MHC was discovered in mouse (1930s) and man (1950s) as the major genetic locus causing complications in experimental and clinical transplantation: graft rejection and graft-versus-host disease.

The Major Histocompatibility Complex (MHC): Discovery and Clinical Relevance

[1] The MHC was discovered in mouse (1930s) and man (1950s) as the major genetic locus causing complications in experimental and clinical transplantation: graft rejection and graft-versus-host disease.

[2] The human MHC is called the HLA complex. The highly polymorphic HLA molecules (HLA-A, HLA-B and HLA-C) were first defined by serology as antigens on the surface of white blood cells: hence the name:
Human Leukocyte Antigen.

The Major Histocompatibility Complex (MHC): Discovery and Clinical Relevance

[1] The MHC was discovered in mouse (1930s) and man (1950s) as the major genetic locus causing complications in experimental and clinical transplantation: graft rejection and graft-versus-host disease.

[2] The human MHC is called the HLA complex. The highly polymorphic HLA molecules (HLA-A, HLA-B and HLA-C) were first defined by serology as antigens on the surface of white blood cells: hence the name: <u>H</u>uman <u>L</u>eukocyte <u>A</u>ntigen.

[3] The HLA complex consists of ~4 megabases on the short arm of chromosome 6, with the six HLA class I genes occupying ~2 megabases.

The Major Histocompatibility Complex (MHC): Discovery and Clinical Relevance

[1] The MHC was discovered in mouse (1930s) and man (1950s) as the major genetic locus causing complications in experimental and clinical transplantation: graft rejection and graft-versus-host disease.

[2] The human MHC is called the HLA complex. The highly polymorphic HLA molecules (HLA-A, HLA-B and HLA-C) were first defined by serology as antigens on the surface of white blood cells: hence the name: Human Leukocyte Antigen.

[3] The HLA complex consists of ~4 megabases on the short arm of chromosome 6, with the six HLA class I genes occupying ~2 megabases.

[4] Because of the importance of HLA matching donor and recipient in clinical transplantation, some 20 million human individuals, representing a wide geographical and ethnical range, have been genotyped for HLA-A, -B, -C.

The Major Histocompatibility Complex (MHC): Discovery and Clinical Relevance

[1] The MHC was discovered in mouse (1930s) and man (1950s) as the major genetic locus causing complications in experimental and clinical transplantation: graft rejection and graft-versus-host disease.

[2] The human MHC is called the HLA complex. The highly polymorphic HLA molecules (HLA-A, HLA-B and HLA-C) were first defined by serology as antigens on the surface of white blood cells: hence the name: Human Leukocyte Antigen.

[3] The HLA complex consists of ~4 megabases on the short arm of chromosome 6, with the six HLA class I genes occupying ~2 megabases.

[4] Because of the importance of HLA matching donor and recipient in clinical transplantation, some 20 million human individuals, representing a wide geographical and ethnical range, have been genotyped for HLA-A, -B, -C.

[5] HLA gene polymorphisms also associate with a wide range of human diseases, frequently giving the strongest genetic association.

MHC molecules bind peptides to become ligands for lymphocyte receptors

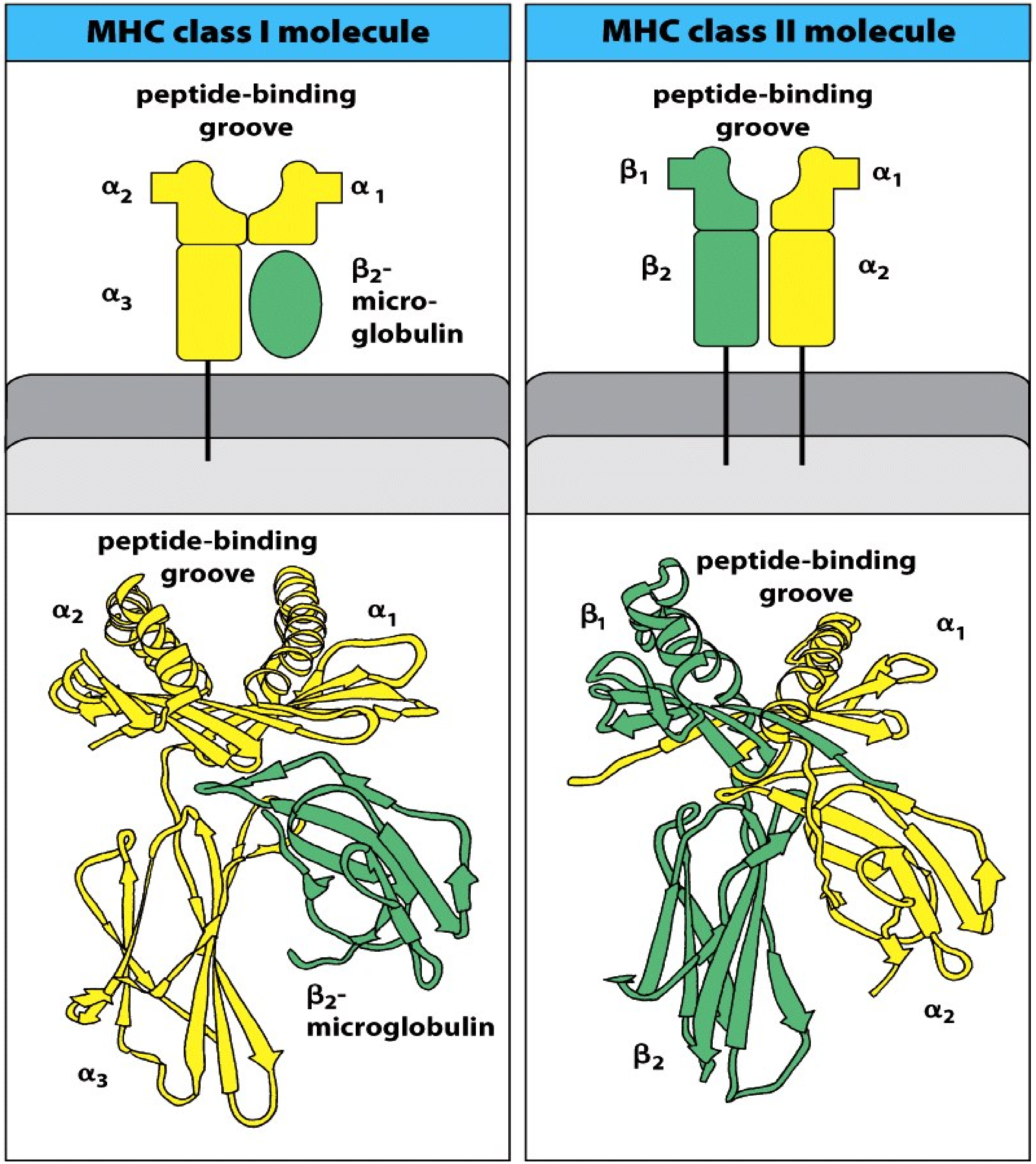


Figure 5.13 The Immune System, 3ed. (© Garland Science 2009)

Bjorkman et al. Nature 1987a & 1987b

Catching the bug of evolution

Brodsky FM, Bodmer WF & Parham P, 1979

Characterization of a monoclonal anti-β_2 microglobulin antibody and its use in the genetic and biochemical analysis of major histocompatibility antigens

European Journal of Immunology 9:536-545

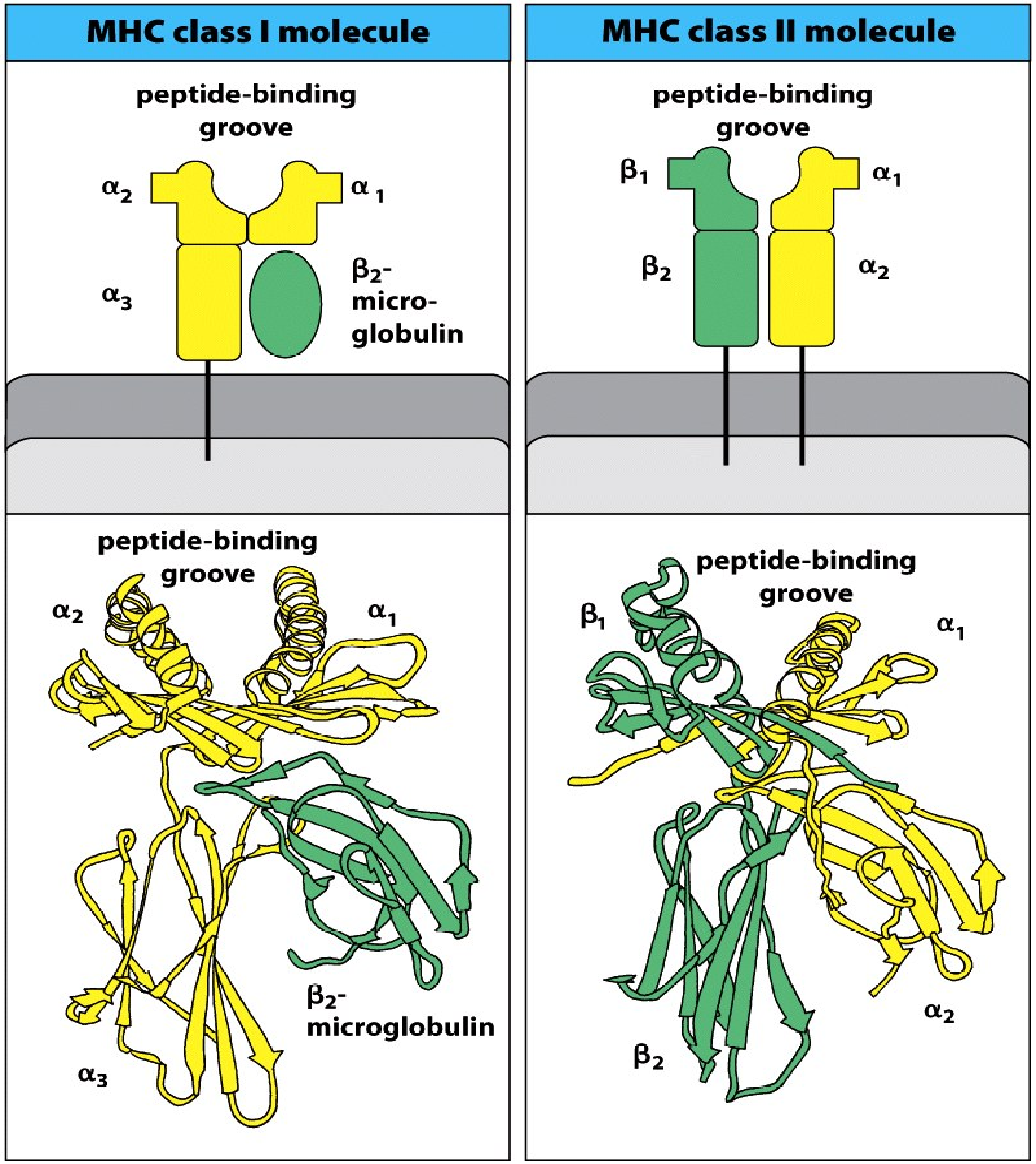


Figure 5.13 The Immune System, 3ed. (© Garland Science 2009)

Bjorkman et al. Nature 1987a & 1987b

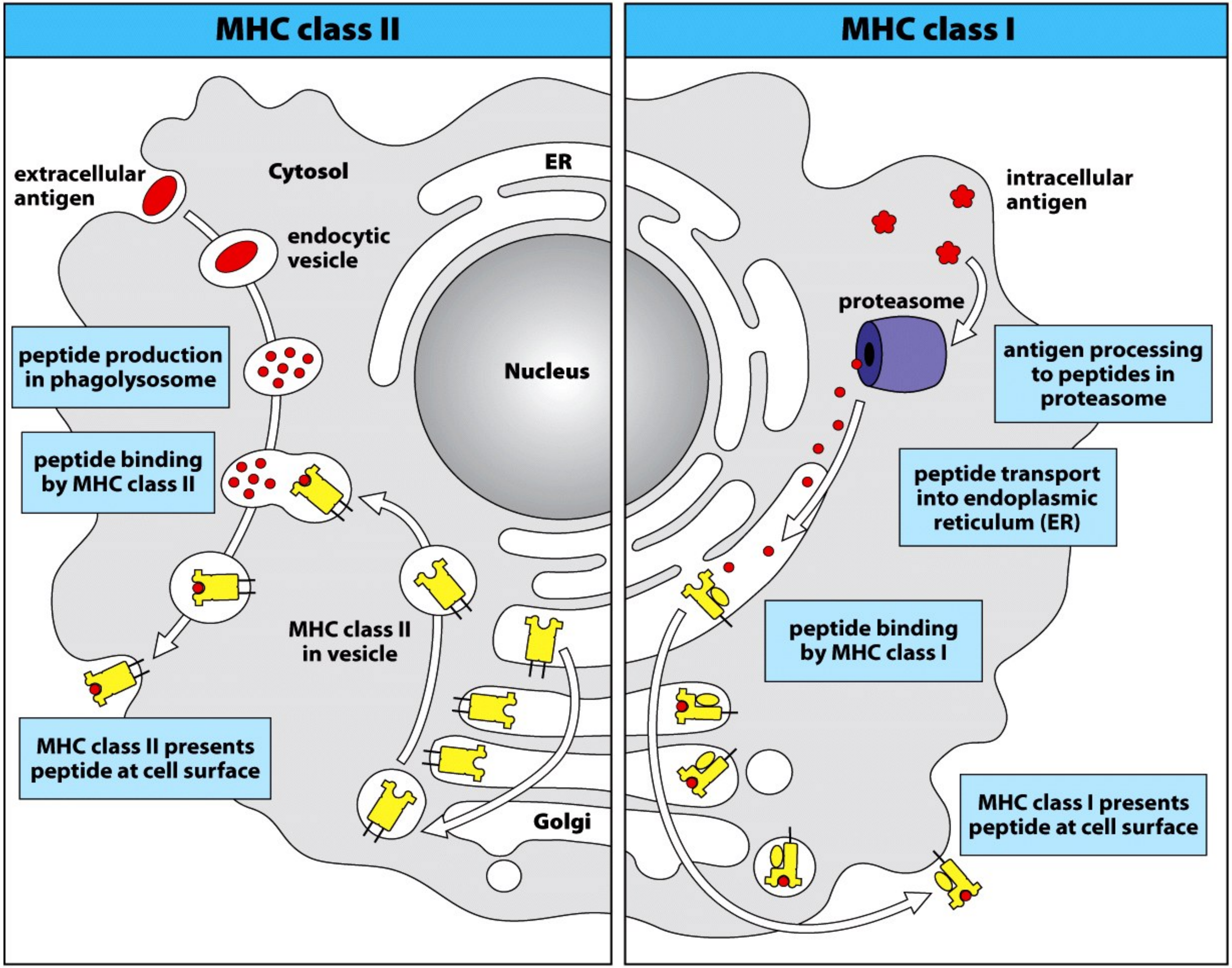
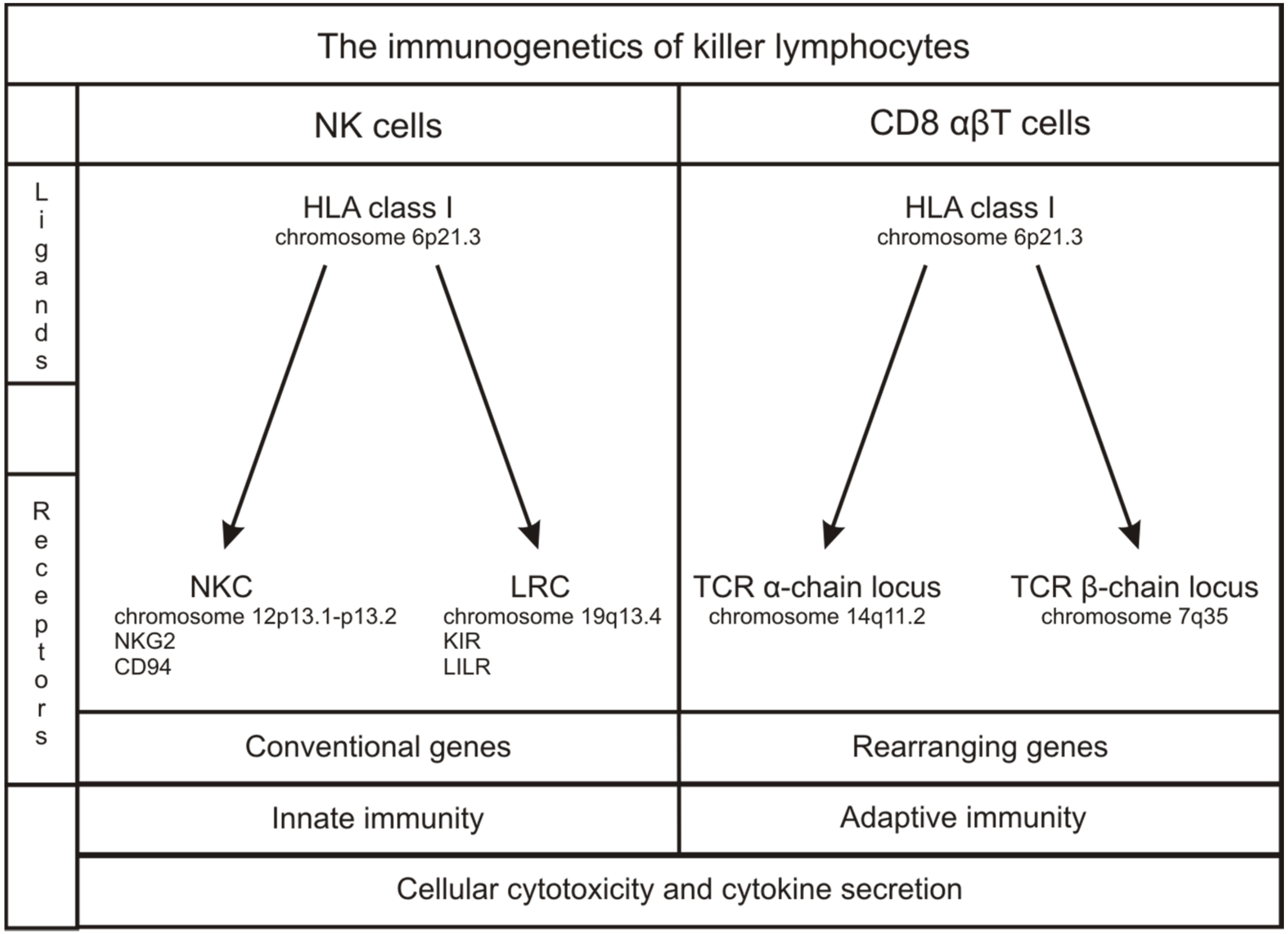


Figure 5.20 The Immune System, 3ed. (© Garland Science 2009)

MHC molecules seek and bind peptides in cellular compartments

NK-cell and T-cell responses are controlled by receptors recognizing MHC class I molecules



The immunogenetics of killer lymphocytes

NK cells

CD8 αβT cells

Ligands

HLA class I
chromosome 6p21.3

HLA class I
chromosome 6p21.3

Receptors

NKC
chromosome 12p13.1-p13.2
NKG2
CD94

LRC
chromosome 19q13.4
KIR
LILR

TCR α-chain locus
chromosome 14q11.2

TCR β-chain locus
chromosome 7q35

Conventional genes

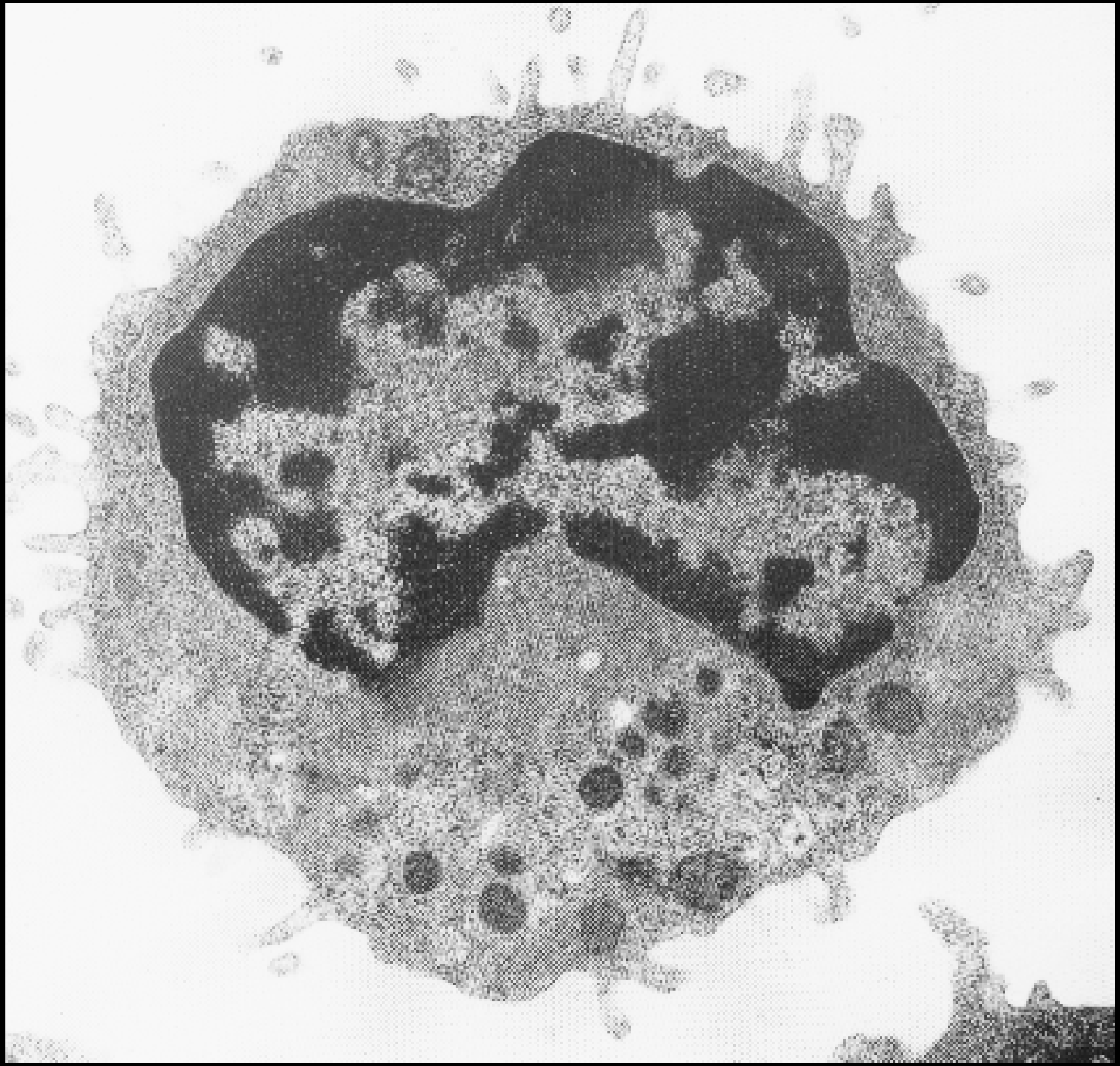
Rearranging genes

Innate immunity

Adaptive immunity

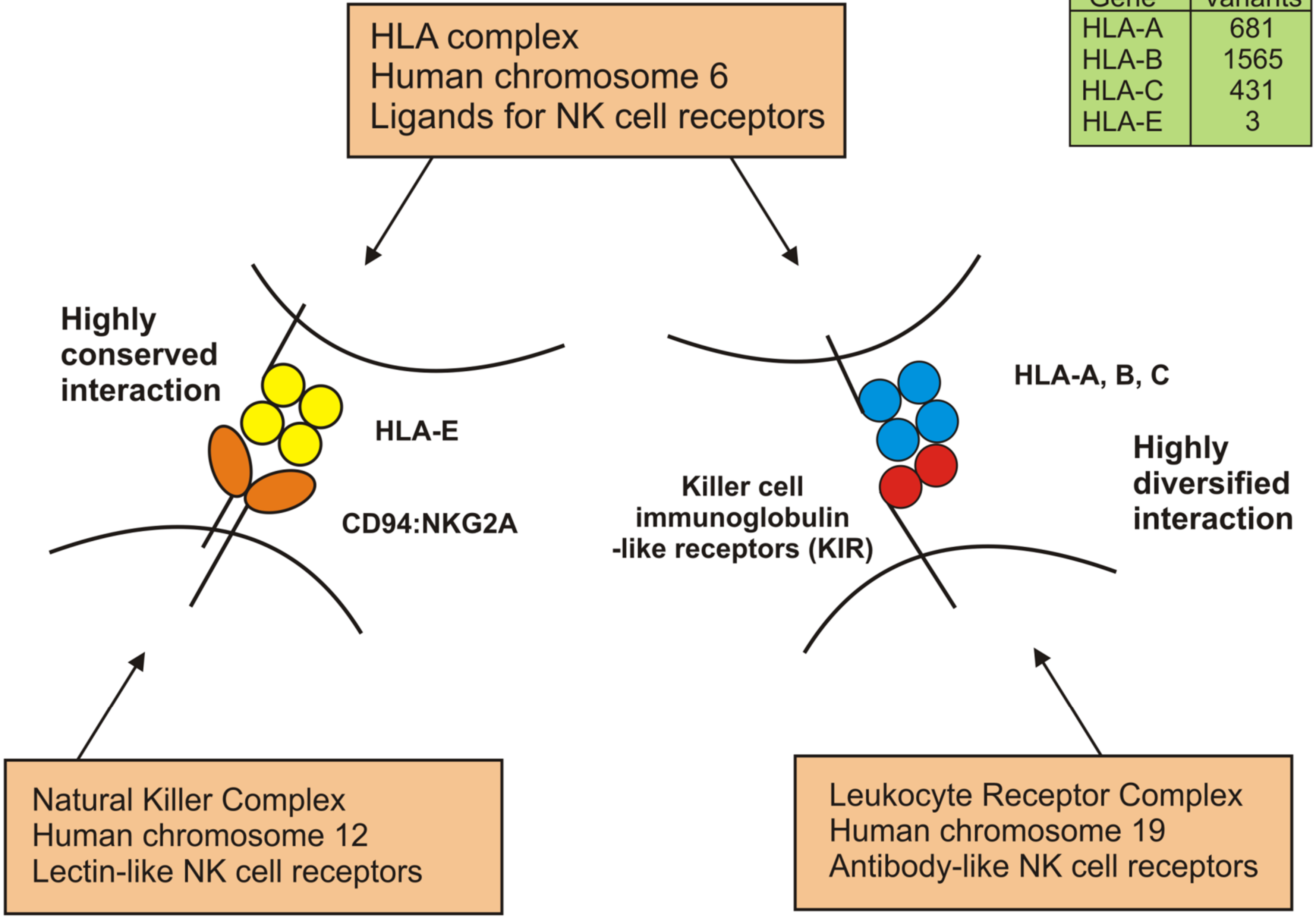
Cellular cytotoxicity and cytokine secretion

A human Natural Killer (NK) cell



Conserved and diverse interactions between HLA class I and NK cell receptors

Gene	Variants
HLA-A	681
HLA-B	1565
HLA-C	431
HLA-E	3



HLA complex
Human chromosome 6
Ligands for NK cell receptors

Natural Killer Complex
Human chromosome 12
Lectin-like NK cell receptors

Leukocyte Receptor Complex
Human chromosome 19
Antibody-like NK cell receptors

By presenting leader-sequence peptides derived from HLA-A, B and C to the inhibitory CD94:NKG2A receptor of NK cells, the HLA-E molecule reports on the health of HLA class I expression.

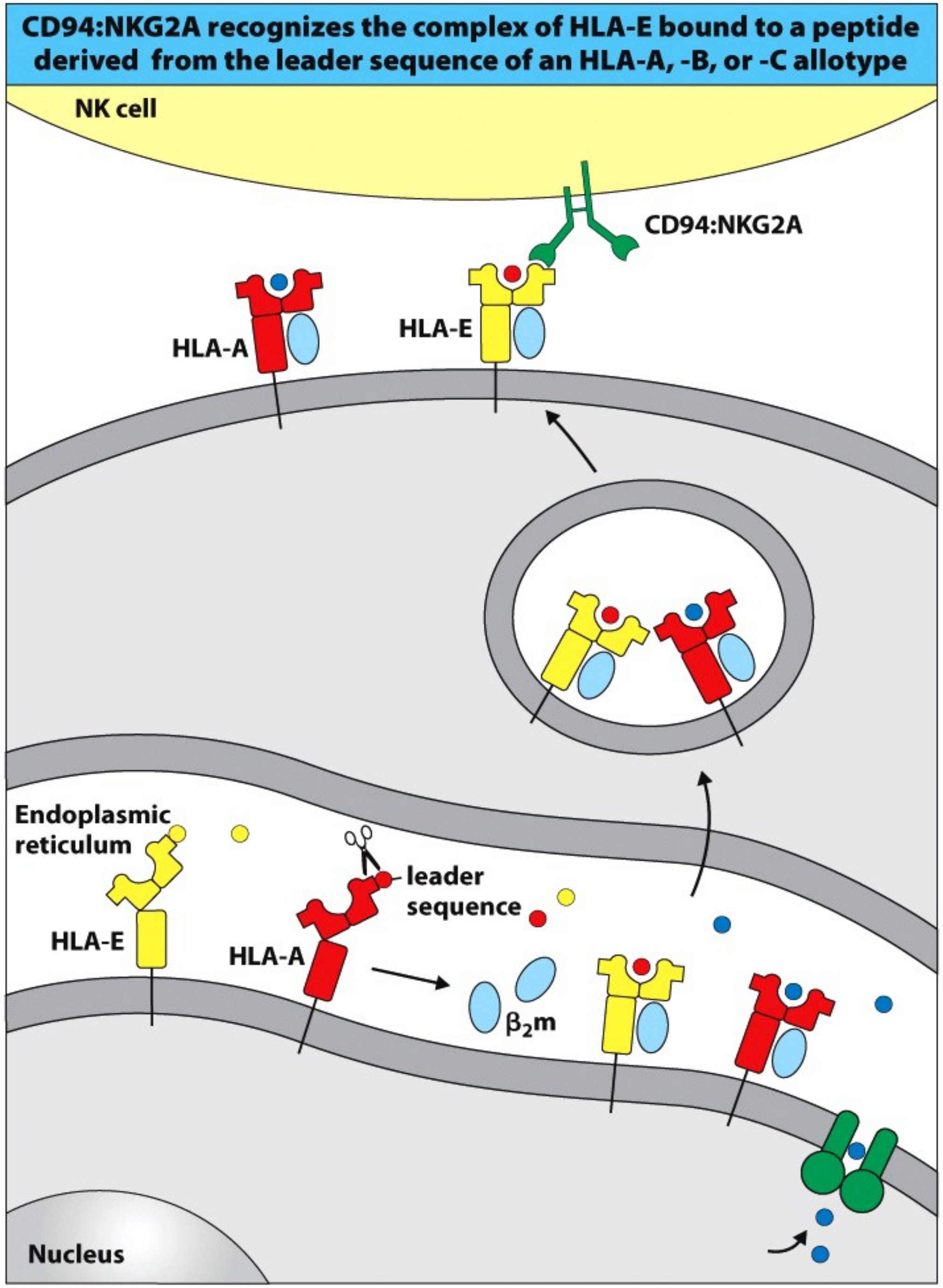
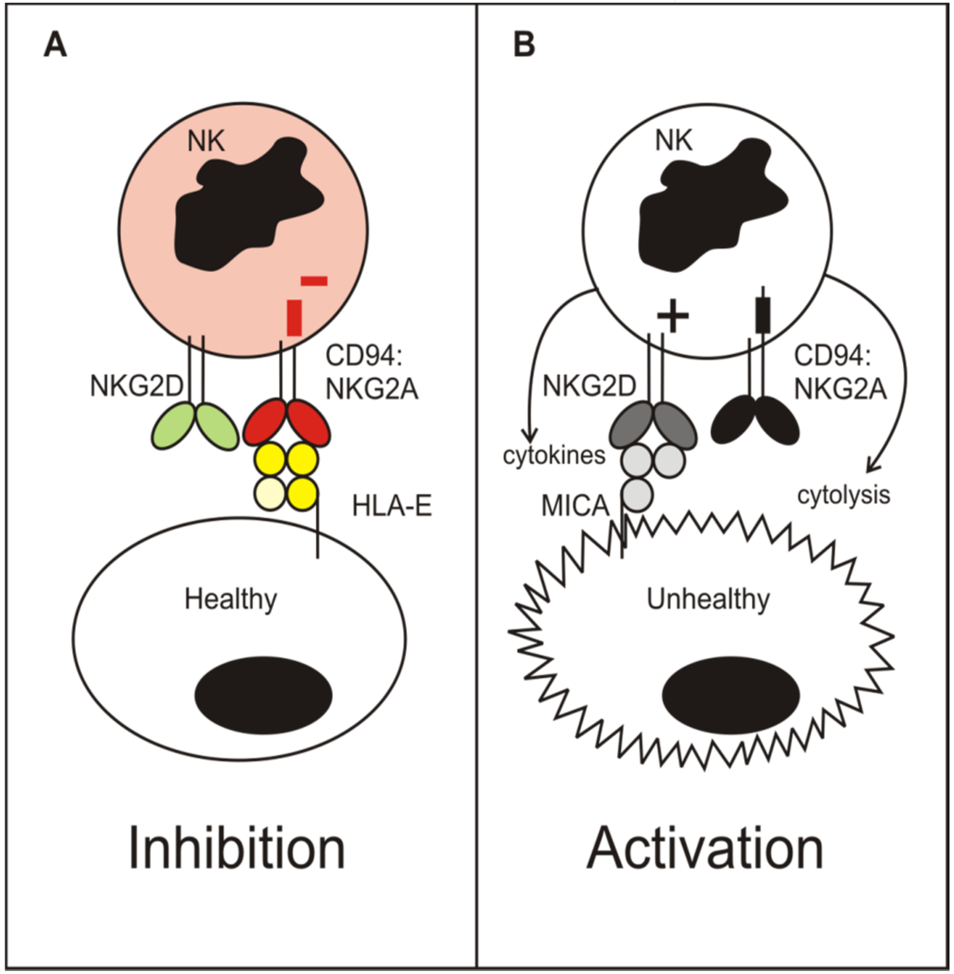

CD94:NKG2A recognizes the complex of HLA-E bound to a peptide derived from the leader sequence of an HLA-A, -B, or -C allotype

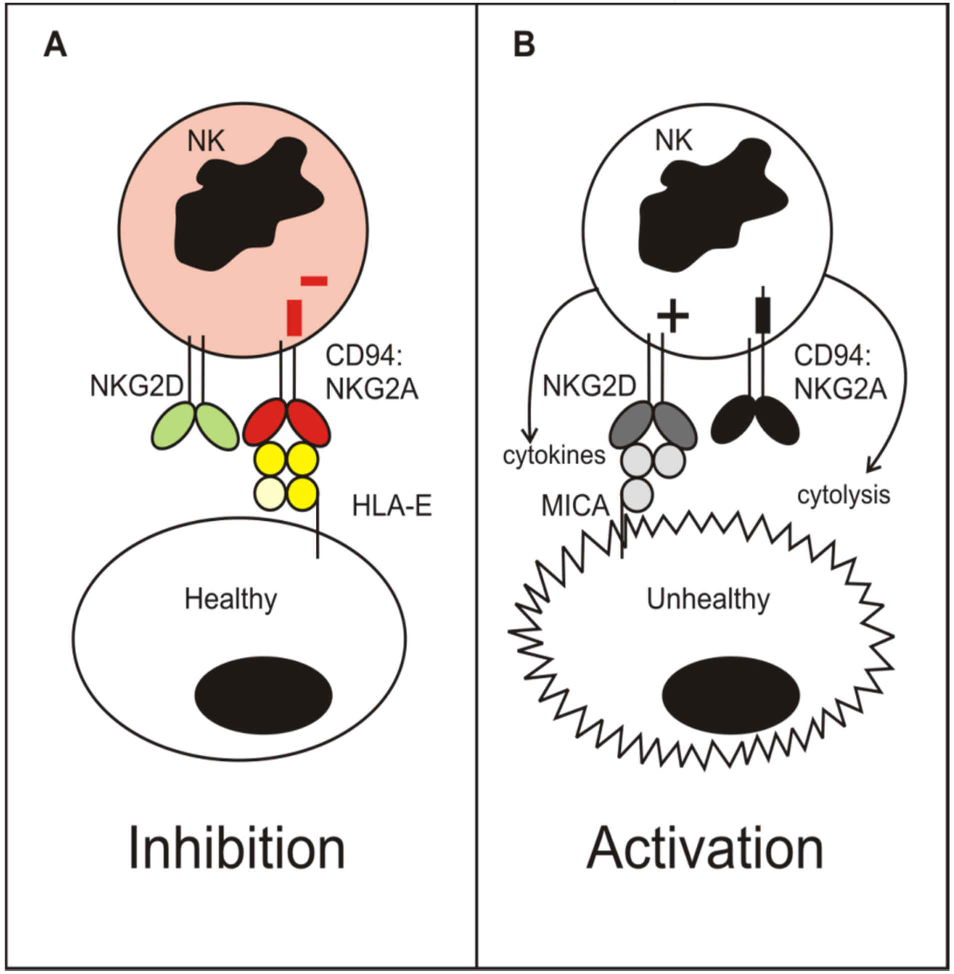
Figure 10.35 The Immune System, 3ed. (© Garland Science 2009)

Inhibitory receptors make NK cells responsive to loss of MHC class I expression



NK cells are inhibited from killing cells that express normal HLA class I.

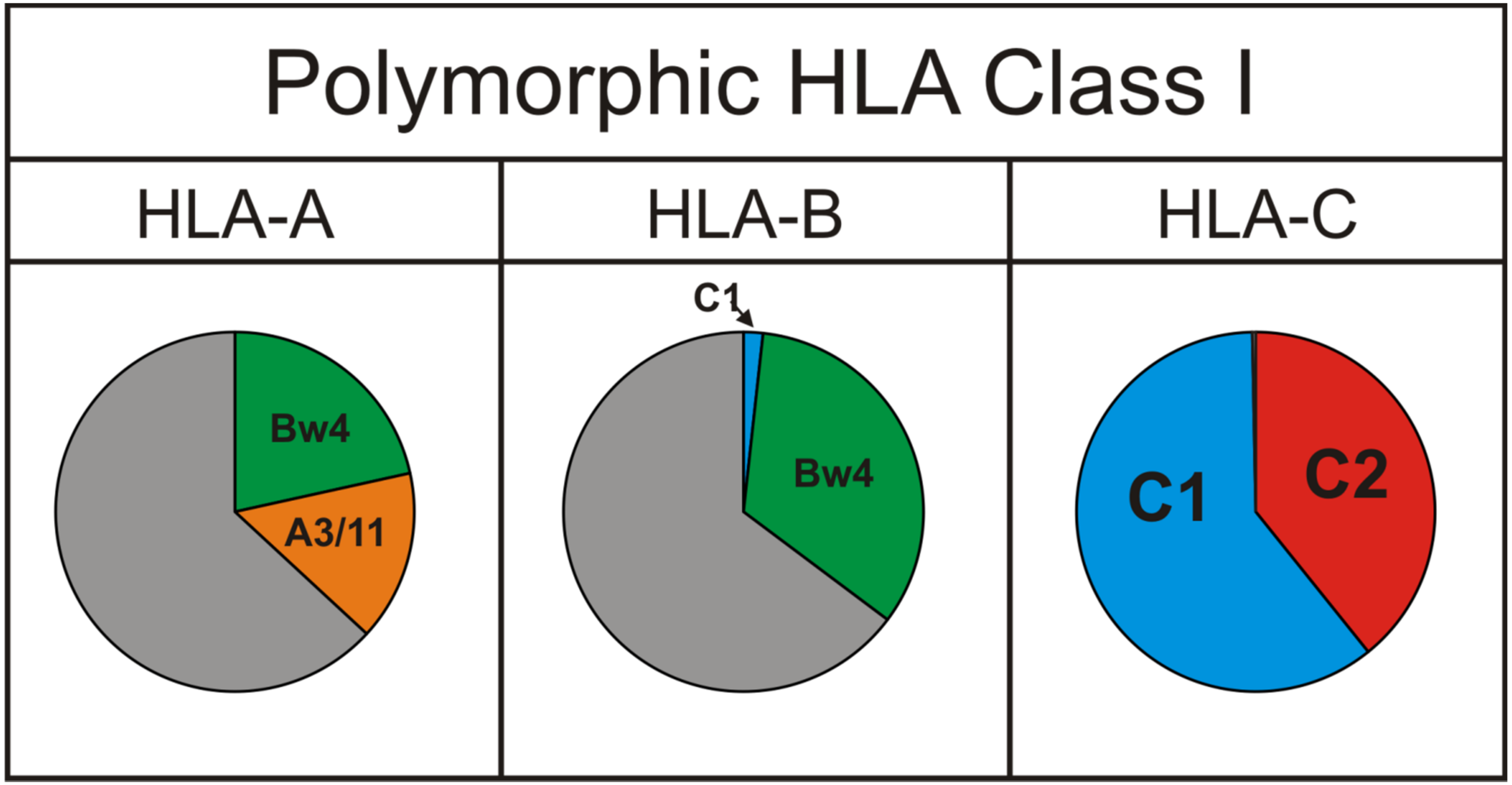
Inhibitory receptors make NK cells responsive to loss of MHC class I expression



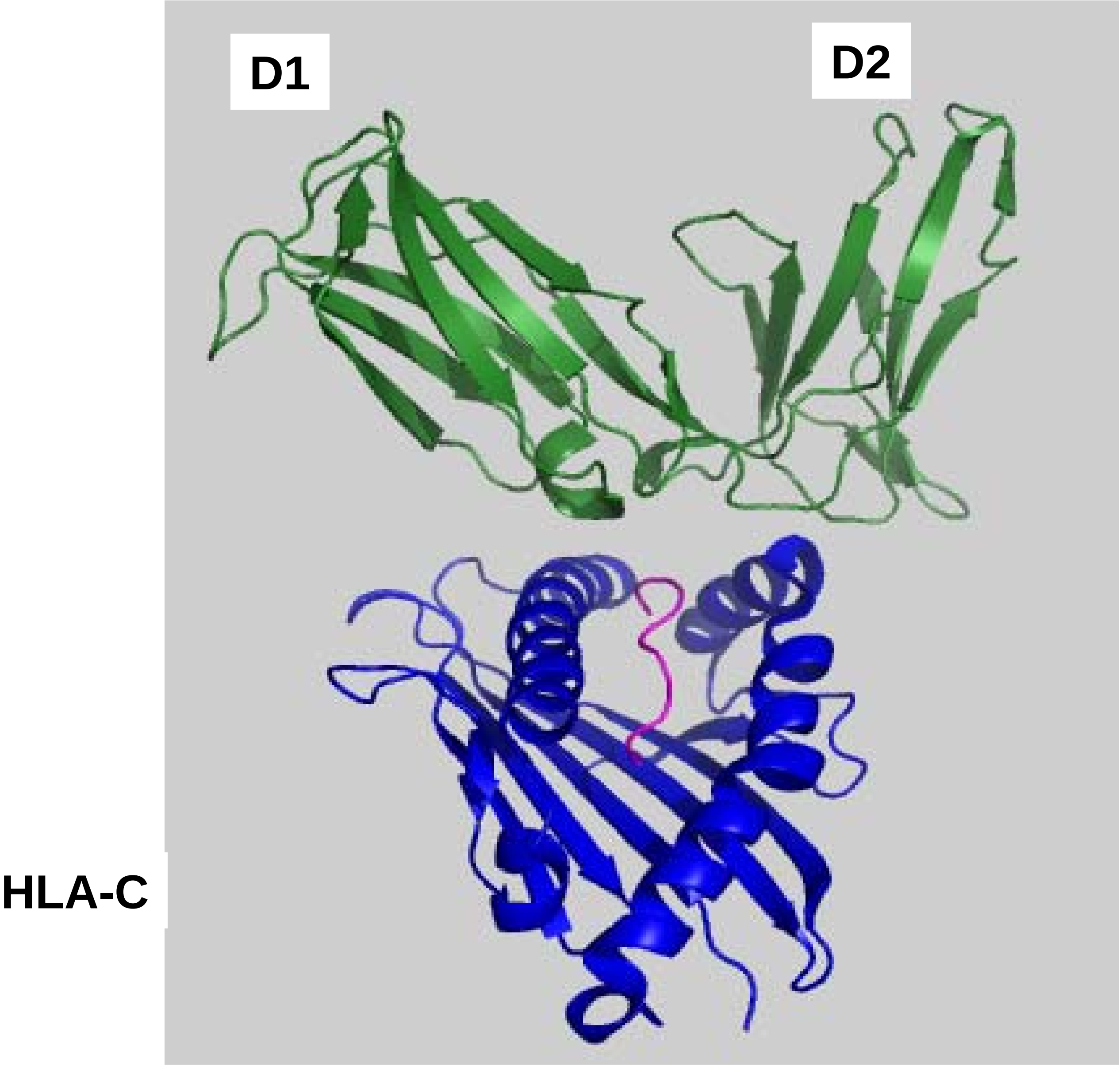
NK cells are inhibited from killing cells that express normal HLA class I.

NK cells are able to kill cells in which the expression is altered by infection or cancer.

KIR Recognize and Distinguish Four Epitopes of HLA-A,-B,and -C



Structure of the complex of KIR2D with HLA class I



KIR and CD8 T-cell receptors have overlapping binding sites on HLA class I that likely impose different selections for change

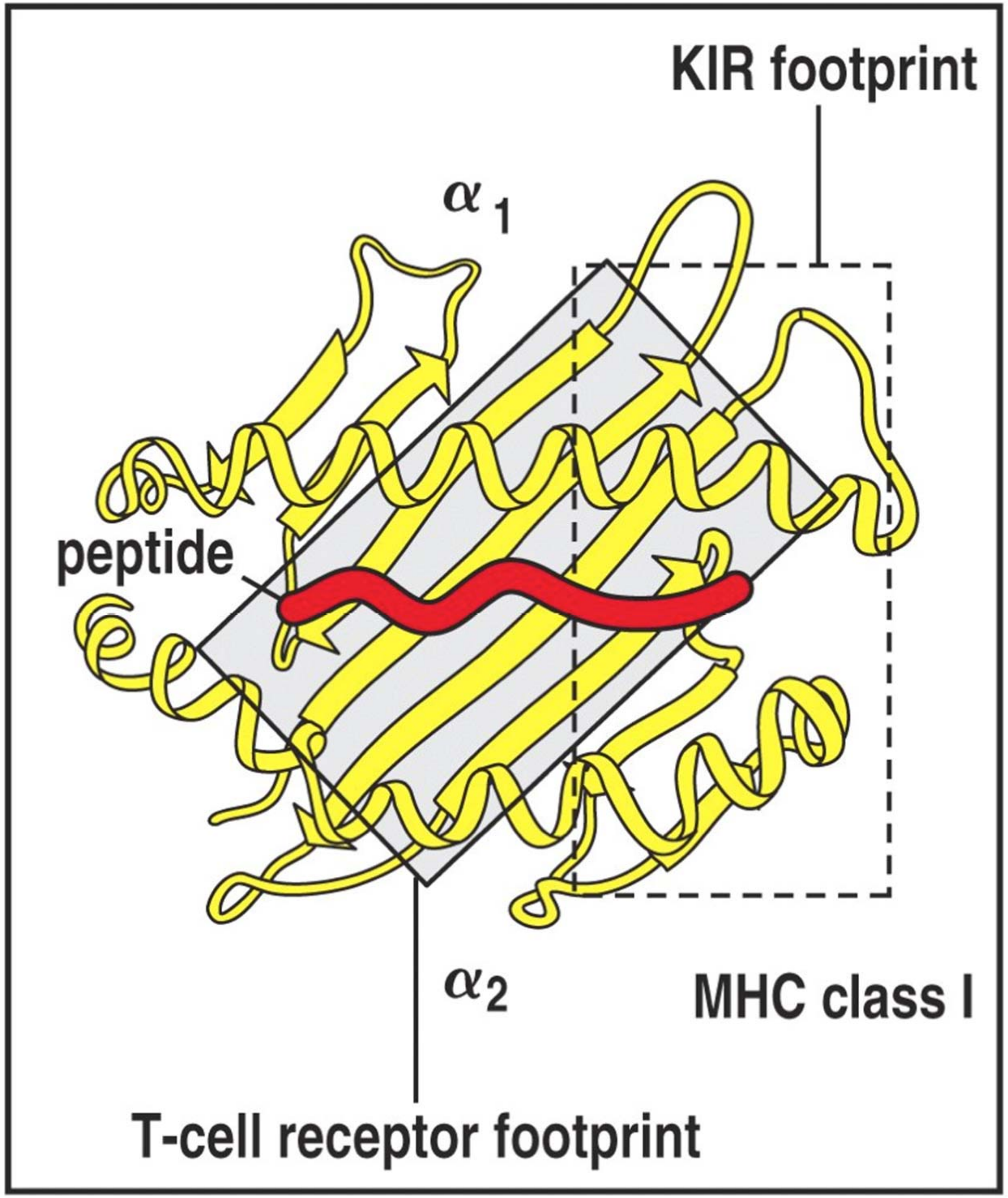
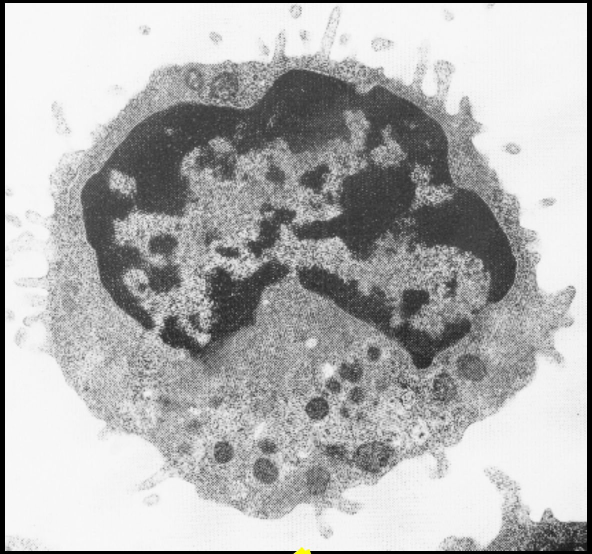


Figure 8-30 The Immune System, 2/e (© Garland Science 2005)

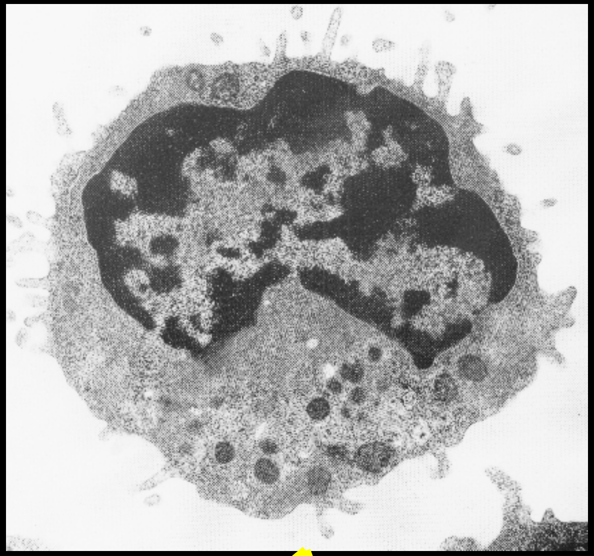
Functions of Natural Killer (NK) cells



Immune system

Reproductive system

Functions of Natural Killer (NK) cells



Immune system

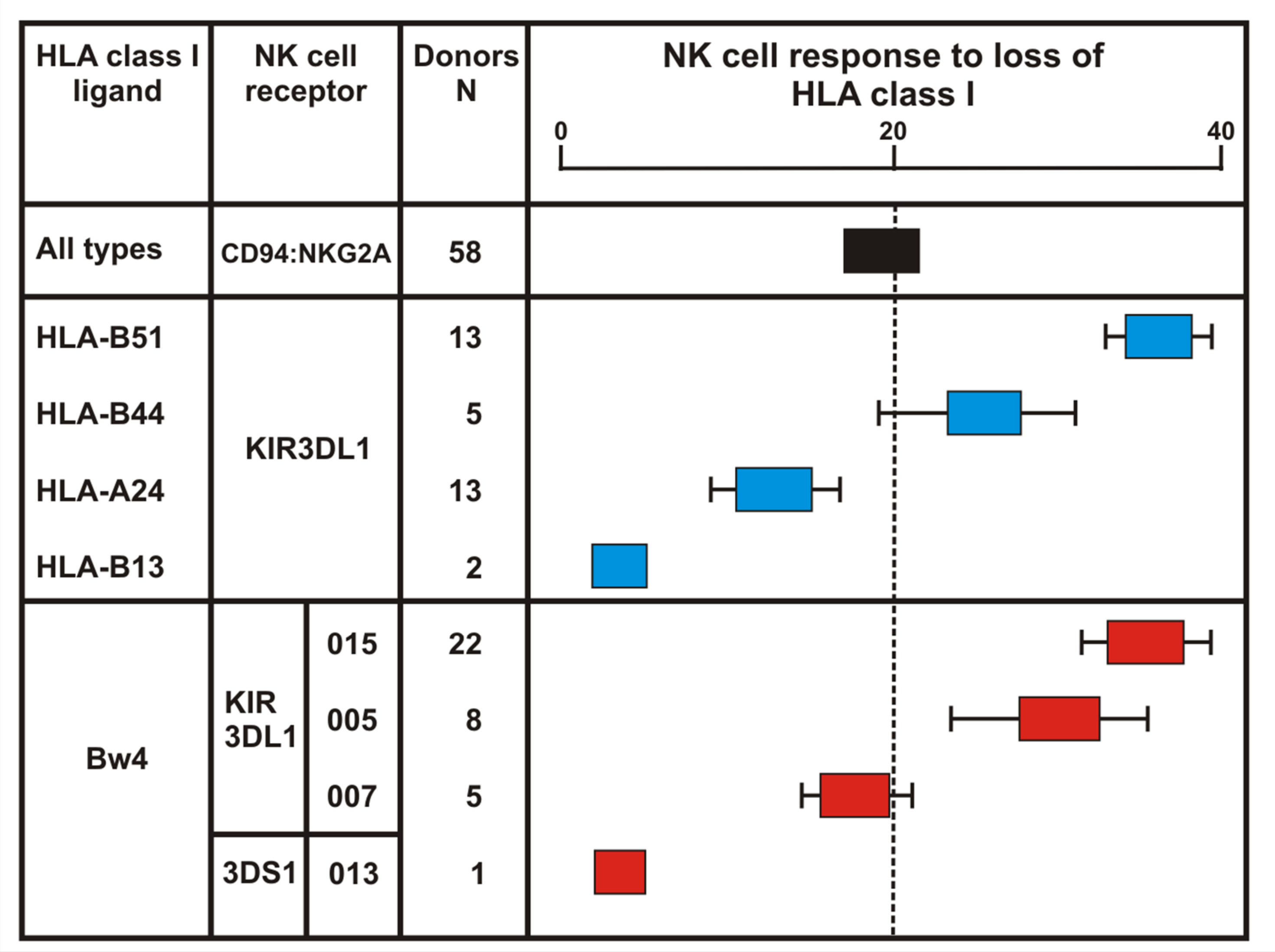
Kill virus-infected cells

and cancerous cells.

Co-operate with dendritic cells

Reproductive system

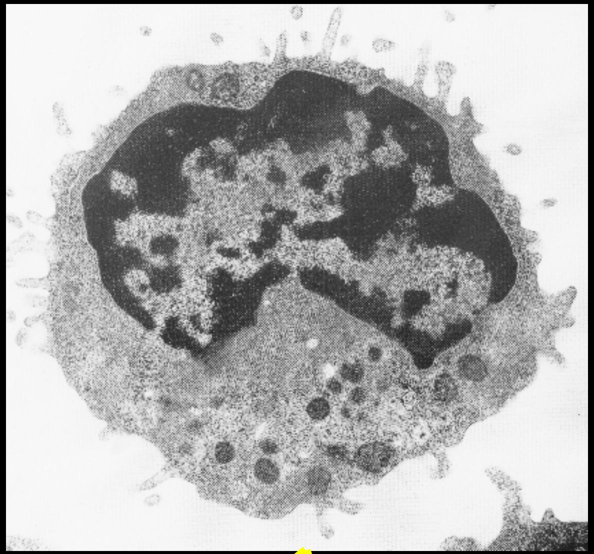
Variability of KIR3DL1-mediated Responses to Absence of Class I, compared to Constancy of CD94:NKG2A

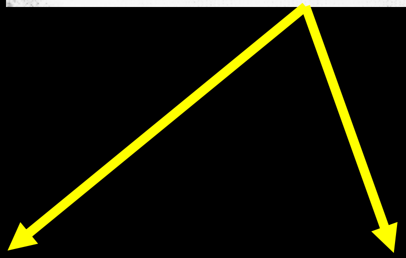


HLA class I ligand	NK cell receptor		Donors N	NK cell response to loss of HLA class I
All types	CD94:NKG2A		58	
HLA-B51	KIR3DL1		13	
HLA-B44			5	
HLA-A24			13	
HLA-B13			2	
Bw4	KIR 3DL1	015	22	
		005	8	
		007	5	
	3DS1	013	1	

Yawata et al 2008, Blood 112: 2369

Functions of Natural Killer (NK) cells





Immune system

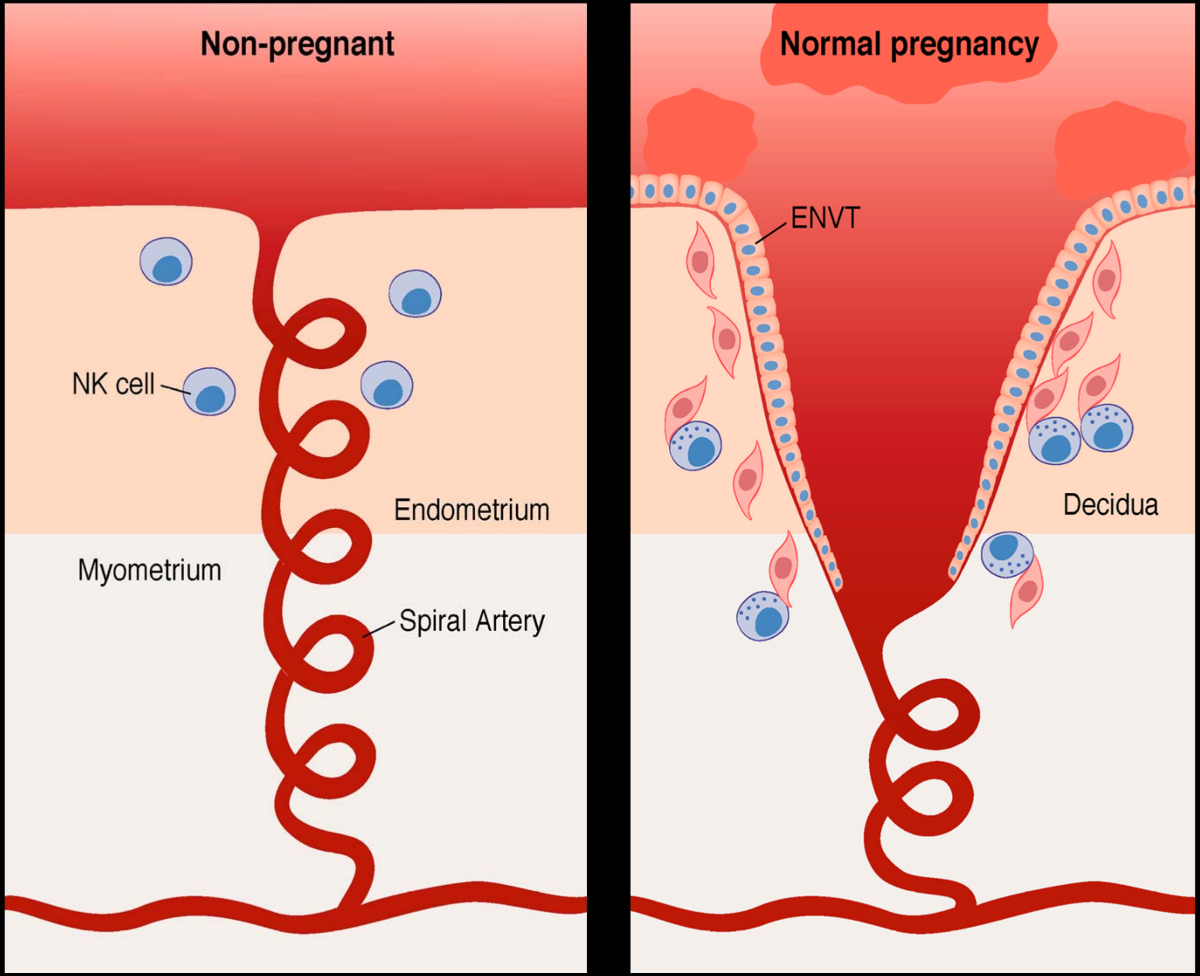
Kill virus-infected cells
and cancerous cells.

Co-operate with dendritic cells

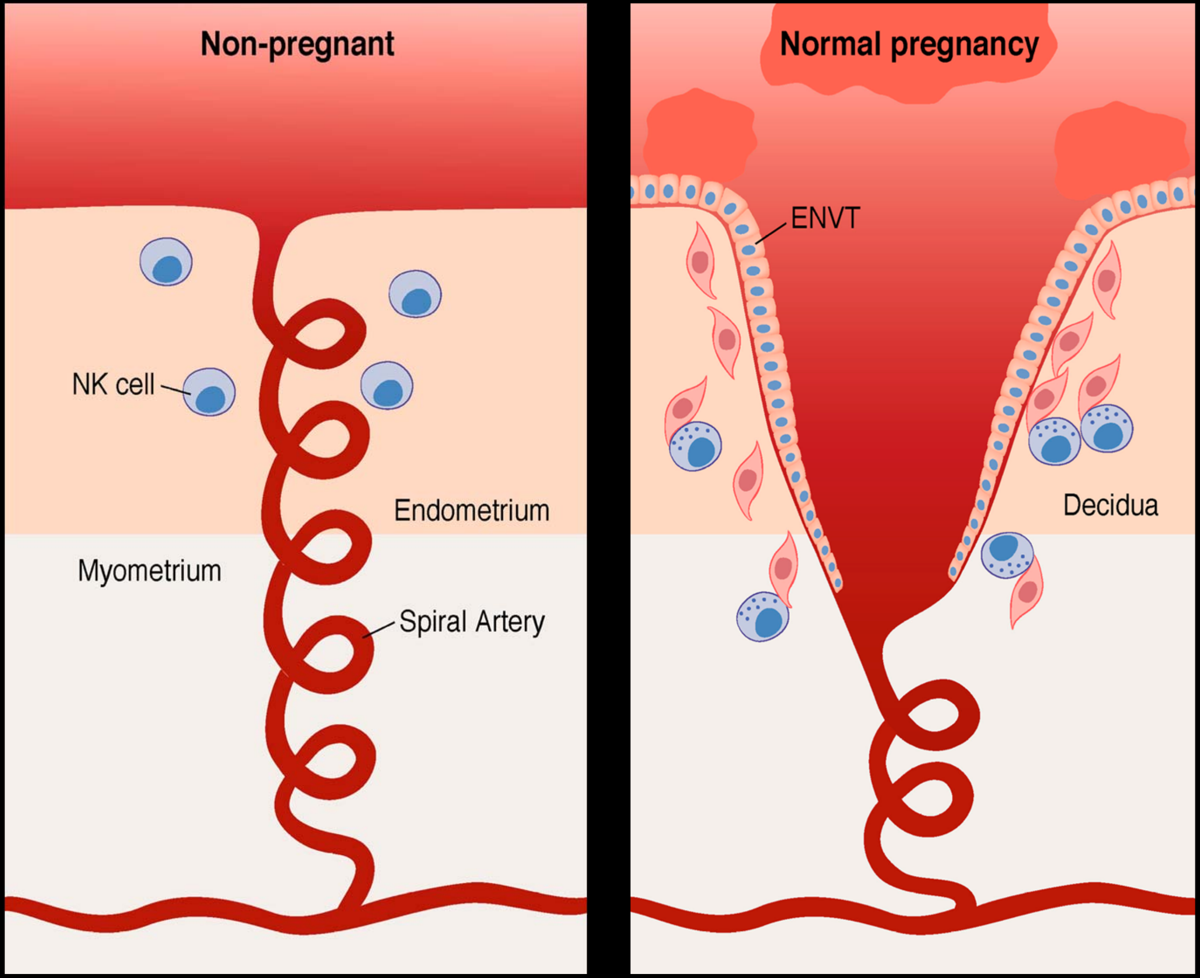
Reproductive system

Maternal uterine NK cells co-operate with fetal extra-villous trophoblast to widen maternal arteries supplying blood to the placenta.

Interactions between fetal trophoblast and maternal uterine NK cells remodel the spiral arteries



Interactions between fetal trophoblast and maternal uterine NK cells remodel the spiral arteries



Extravillous trophoblast expresses HLA-C, -E and G but not HLA-A and -B

The Extraordinary Immunogenetics of Natural Killer (NK) Cell Receptors and Major Histocompatibility Complex (MHC) Class I Ligands

[2] Co-evolution of variable NK cell receptors with MHC class I.

Genealogy of the C57 Black Mouse

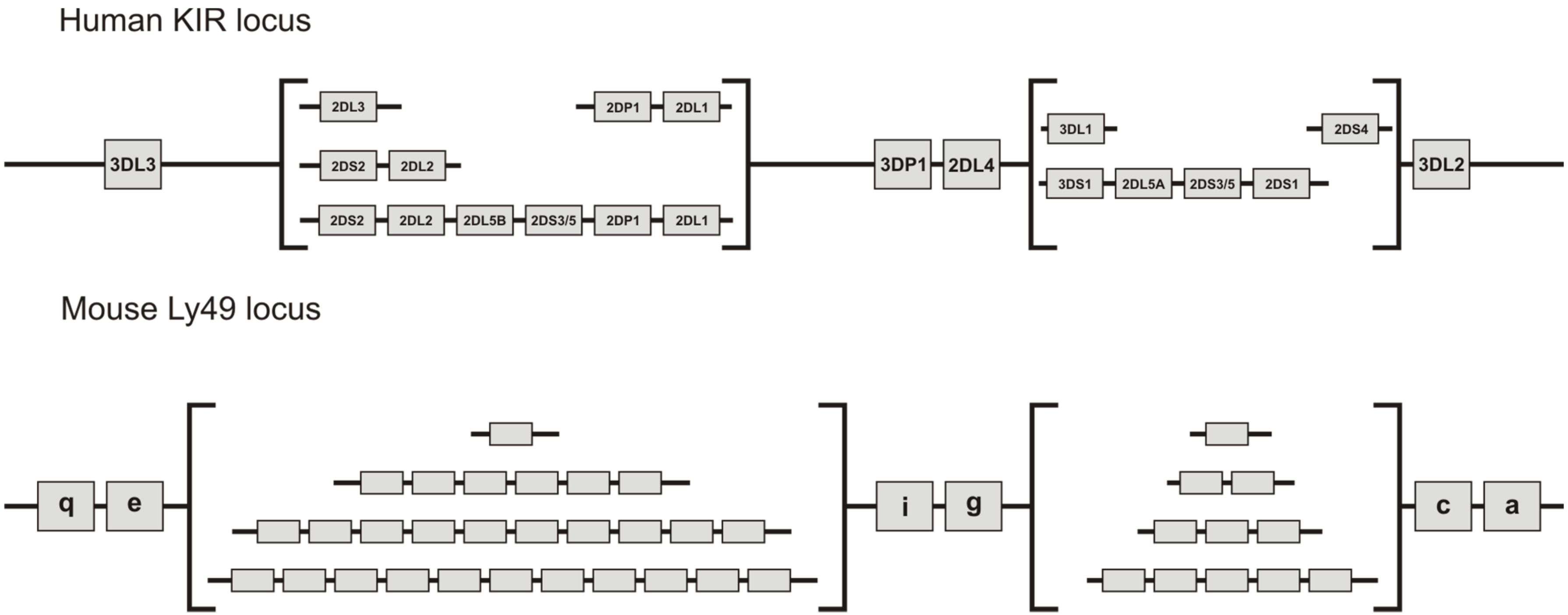
Chinese mouse fanciers
centuries ↓
Japanese mouse fanciers
19th century ↓
English mouse fanciers
1900-1918 ↓
American mouse fanciers
Ms. Abbie Lathrop, Granby, MA
mouse farmer

Interbreeding mice of different species

↓
Clarence Cook Little
Geneticist
↓
1921 Black subline
↓
1929 Jackson Laboratory founded
↓
1937 Black subline 6
↓
1947 C57 BL/6J

Inbred strains retain genes originating from several species of mice

Unexpectedly, the variable NK-cell Receptors of humans and mice were found to have evolved by convergent evolution

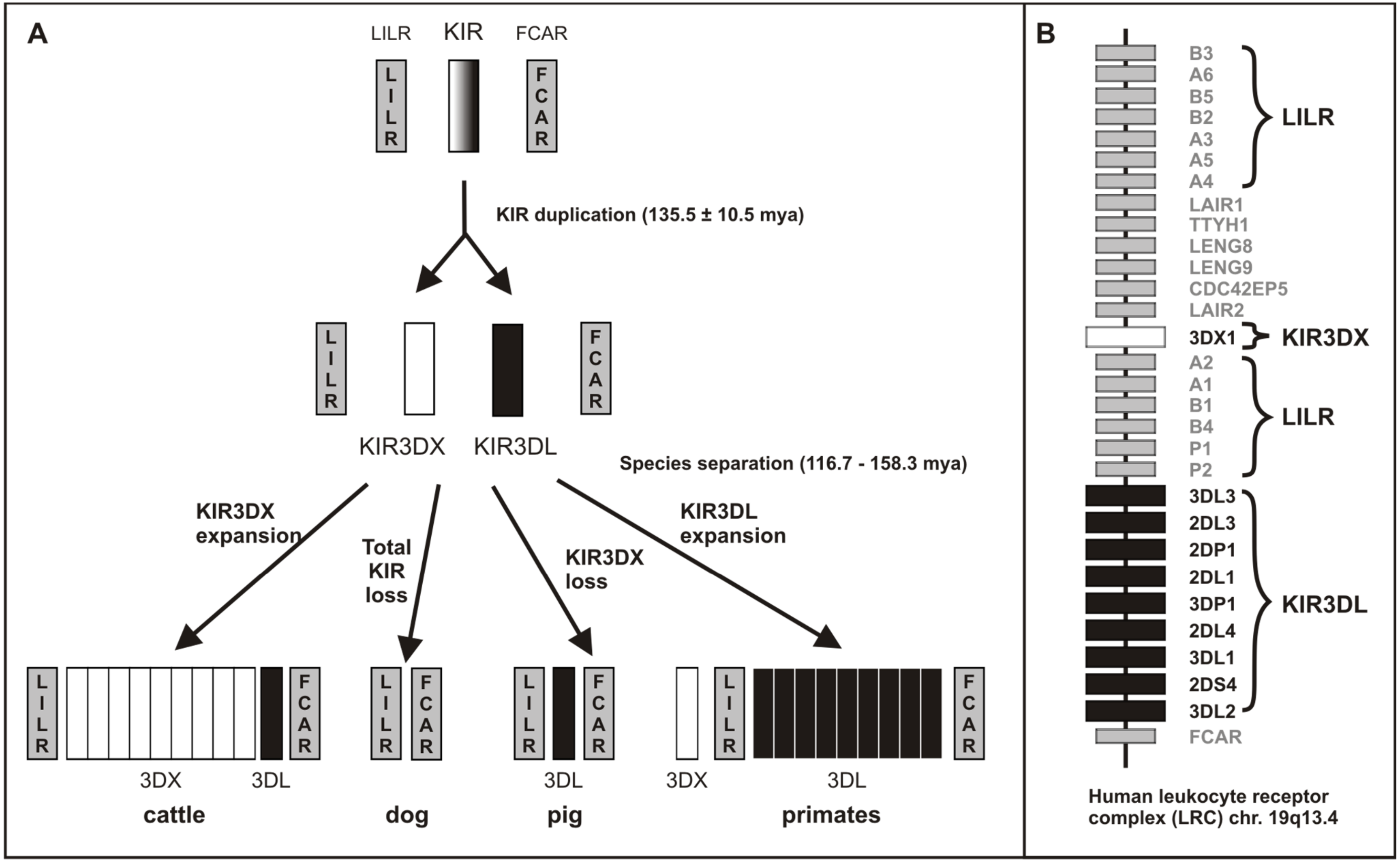


In common: MHC class I ligands,variegated expression, signalling,education, gene organisation.

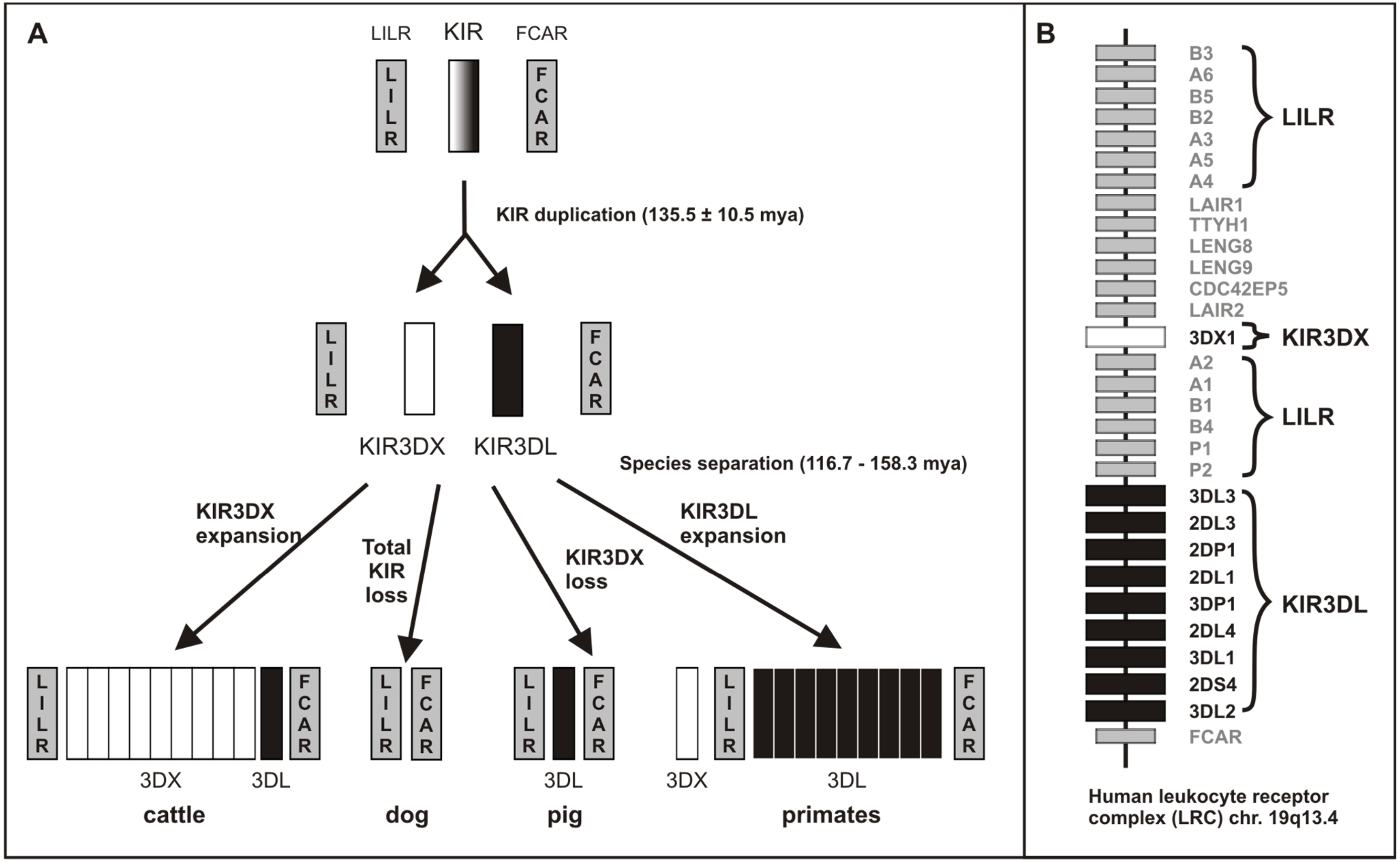
Different: binding site on MHC class I, peptide dependence, structure, genomic location, origin.

Counterparts to the human *KIR* family of NK-cell receptor are found only in simian primates

Cattle and deer independently evolved a KIR gene family, but from a different progenitor

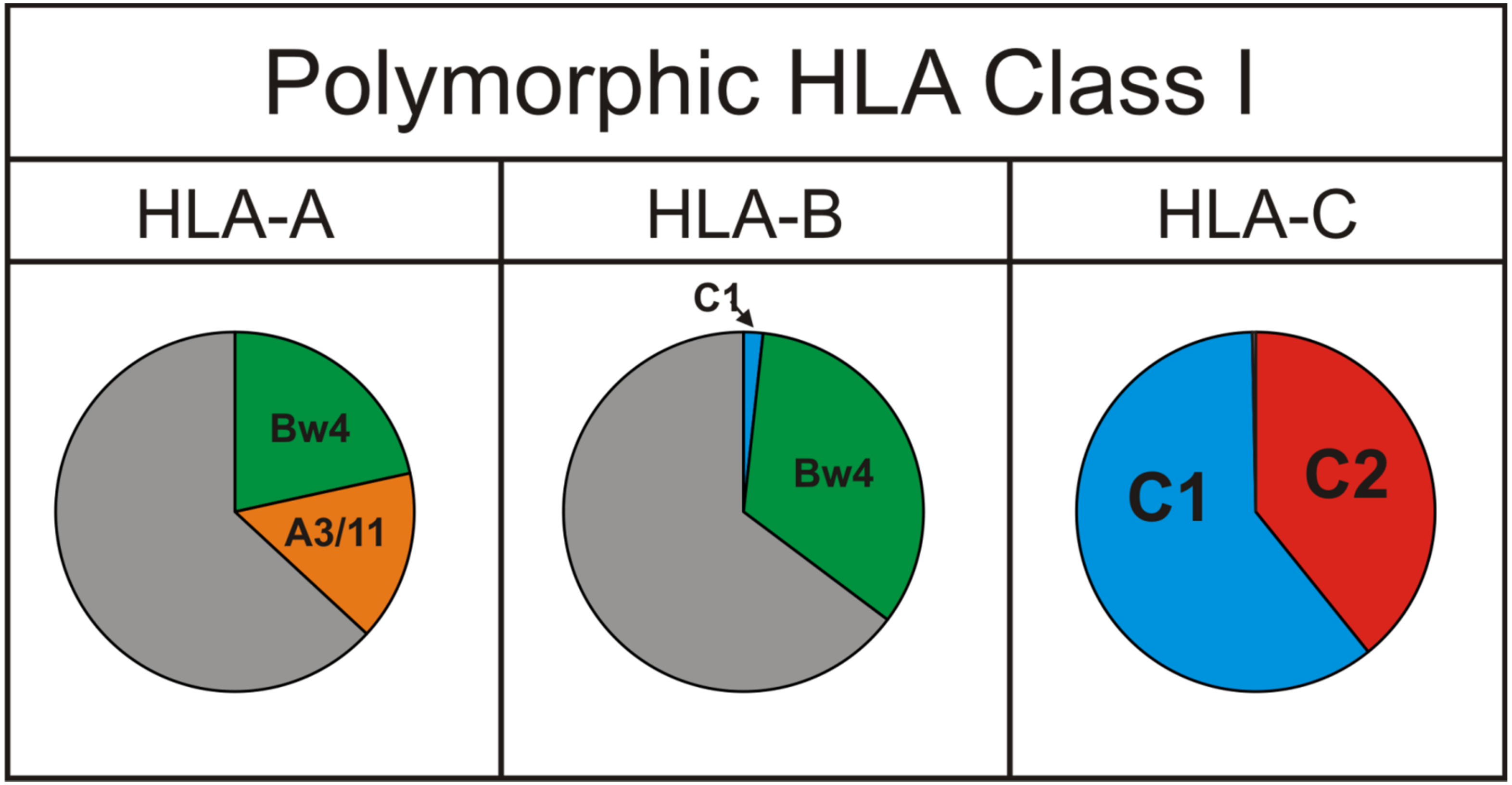


Cattle and deer independently evolved a KIR gene family, but from a different progenitor

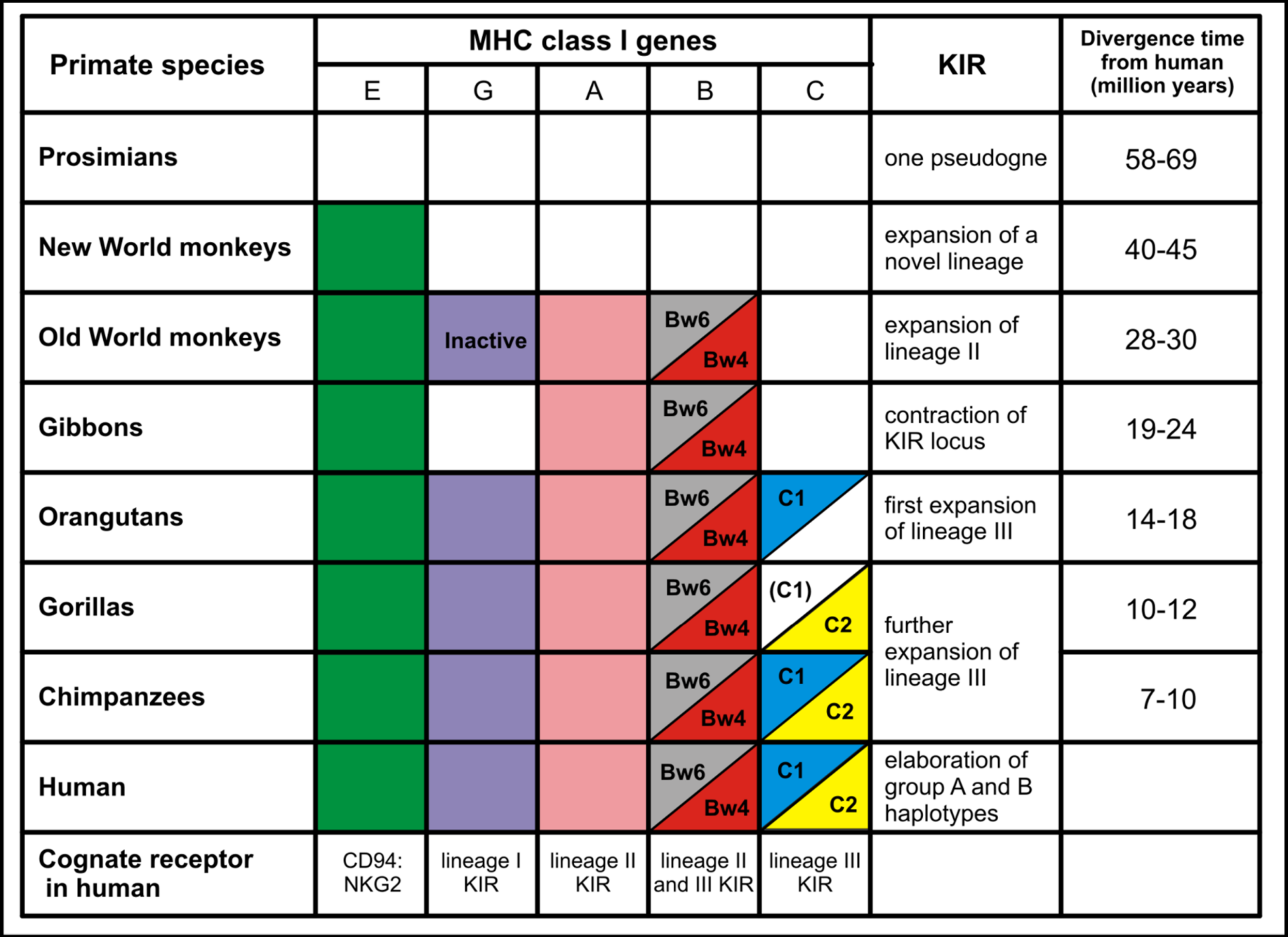


Horses have an expanded Ly49 family (odd toed).

Four Epitopes of HLA-A,-B,and -C are Recognised by KIR



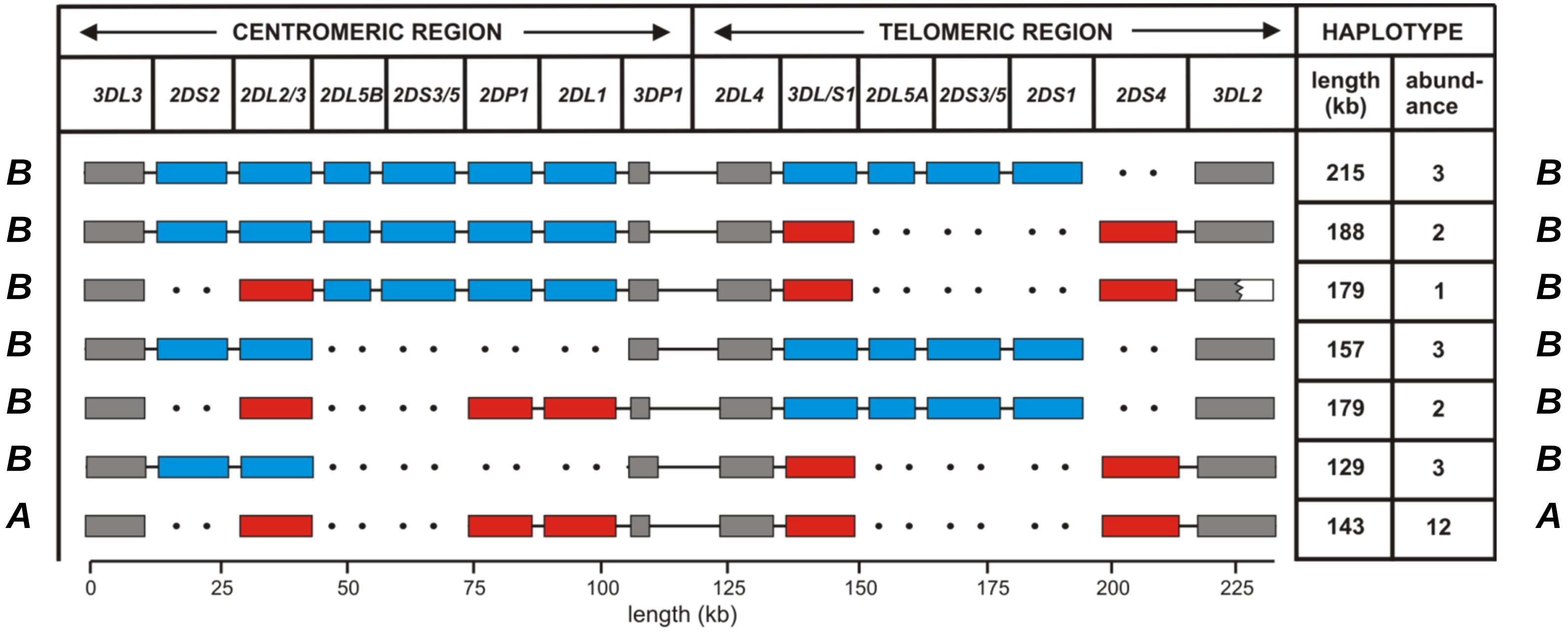
Co-evolution of KIR with the MHC Class I Epitopes they Recognize



Primate species	MHC class I genes					KIR	Divergence time from human (million years)
	E	G	A	B	C		
Prosimians						one pseudogne	58-69
New World monkeys	🟩					expansion of a novel lineage	40-45
Old World monkeys	🟩	🟪 **Inactive**	🟥	**Bw6** **Bw4**		expansion of lineage II	28-30
Gibbons	🟩		🟥	**Bw6** **Bw4**		contraction of KIR locus	19-24
Orangutans	🟩	🟪	🟥	**Bw6** **Bw4**	**C1**	first expansion of lineage III	14-18
Gorillas	🟩	🟪	🟥	**Bw6** **Bw4**	**(C1)** **C2**	further expansion of lineage III	10-12
Chimpanzees	🟩	🟪	🟥	**Bw6** **Bw4**	**C1** **C2**		7-10
Human	🟩	🟪	🟥	**Bw6** **Bw4**	**C1** **C2**	elaboration of group A and B haplotypes	
Cognate receptor in human	CD94: NKG2	lineage I KIR	lineage II KIR	lineage II and III KIR	lineage III KIR		

Parham et al 2010 J Med Primatology.

Gene-content diversity uniquely divides human *KIR* haplotypes into two functional groups: *A* and *B*



	length (kb)	abund-ance	
B	215	3	B
B	188	2	B
B	179	1	B
B	157	3	B
B	179	2	B
B	129	3	B
A	143	12	A

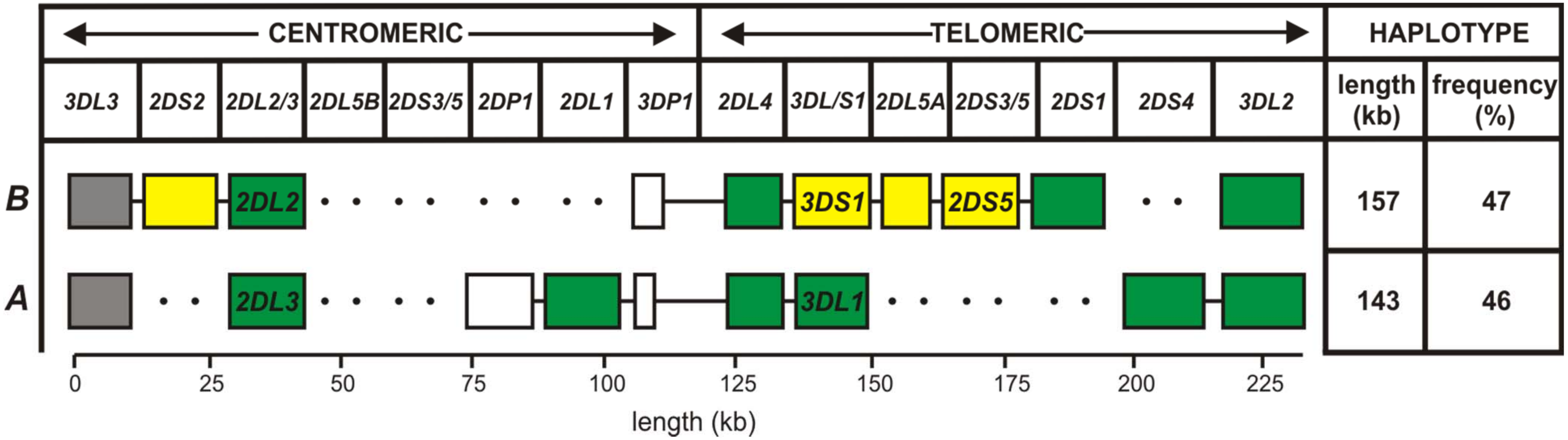
Key:
- ⬛ conserved ‘framework’ KIR genes
- 🟥 KIR genes/alleles characteristic of A haplotypes
- 🟦 KIR genes/alleles characteristic of B haplotypes

Pyo, Guethlein et al PLoS One 2011

Allelic polymorphism combines with gene content diversity to individualize human KIR genotypes.

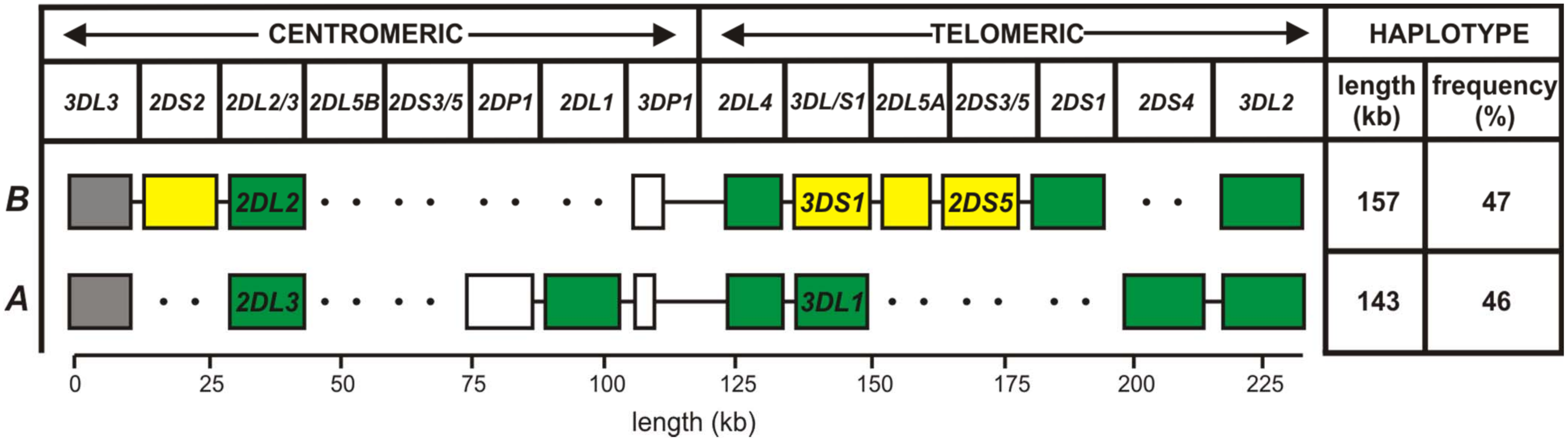
	KIR genes														
	3DL3	2DS2	2DL2L3	2DL5B	2DS3/5	2DL1	2DP1	3DP1	2DL4	3DL1/S1	2DL5A	2DS3/5	2DS1	2DS4	3DL2
1	*00301	*00101	*001	*00201	3*00103	*00401	*00102	*00301	*00501	*01301	*00101	5*002	*00201		*00701
2	*00301	*00101	*001	*00201	3*00103	*00401	*00102	*00301	*00501	*01301	*00501	3*002	*00201		*00701
3	*00301	*00101	*001	*00201	3*00103	*00401	*00102	*00301	*00501	*01301	*00501	3*002	*00201		*00701
4	*00301	*00101	*003					*002	*00501	*01301	*00101	5*002	*00201		*007
5	*00801	*00101	*003					N6	*00501	*01301	*00501	3*002	*00201		*00701
6	*01402	*00101	*003					N6	*00501	*01301	*00101	5*002	*00201		*018
7	*00301	*00101	*001	*00201	3*00103	*007	*00102	*00301	*00602	*007				*004	*008
8	*01402	*00101	*001	*00801	5*007	*00401	N5	N4	*011	*00501				N2	*010
9	*00402	*00101	*001	*004	5*006	N2	N6	N4	*011	*00501				N2	*010
10	part		N1	*00601	5*004	*010	N7	N7	*00802	N2				*006	N5
11	*00402	*00101	*003					N5	*00102	*029				*00101	*002
12	*01402	*00101	*001					*001	*00602	*007				*004	*008
13	N2	*00101	*003					N6	*00801	*00101				*003	*00101
14	*00901		*001			N1	*00201	*00302	*00103	*014	*00101	5*002	*00201		N3
15	*010		*001			*00302	*00201	*00302	*00501	*01301	*00501	3*002	*00201		*00701
16	*00201		*001			*00302	*00201	*00302	*00801	*00101				*003	*00101
17	*00206		*001			*00302	N1	N1	*00102	*01502				*00101	*002
18	*00802		*001			*00302	*00201	*00302	*00102	*01502				*00101	*002
19	*00901		*001			*00302	*00201	*00302	*00103	*025				*00101	part
20	*00901		*001			*00302	*00201	*00302	*011	*00501				N1	N1
21	*00901		*001			*00302	N2	*00302	*00103	*008				*003	*00901
22	*00901		*001			*00302	*00201	N2	*00103	*01701				*00101	N2
23	*012		*001			*00302	*00201	N3	*011	*00501				N2	*010
24	N1		*001			*00302	*00201	*00302	*00102	*029				*00101	*002
25	*00101		*002			*002	N3	*006	*00103	N1				*00101	N4
26	*019		*002			*002	*003	*006	*00802	*00401				*006	*005
27	*005		*006			*00303	N4	*00302	*00103	*01502				*00101	*002

KIR in Yucpa Amerindians: a population surviving many episodes of epidemic disease and population bottleneck



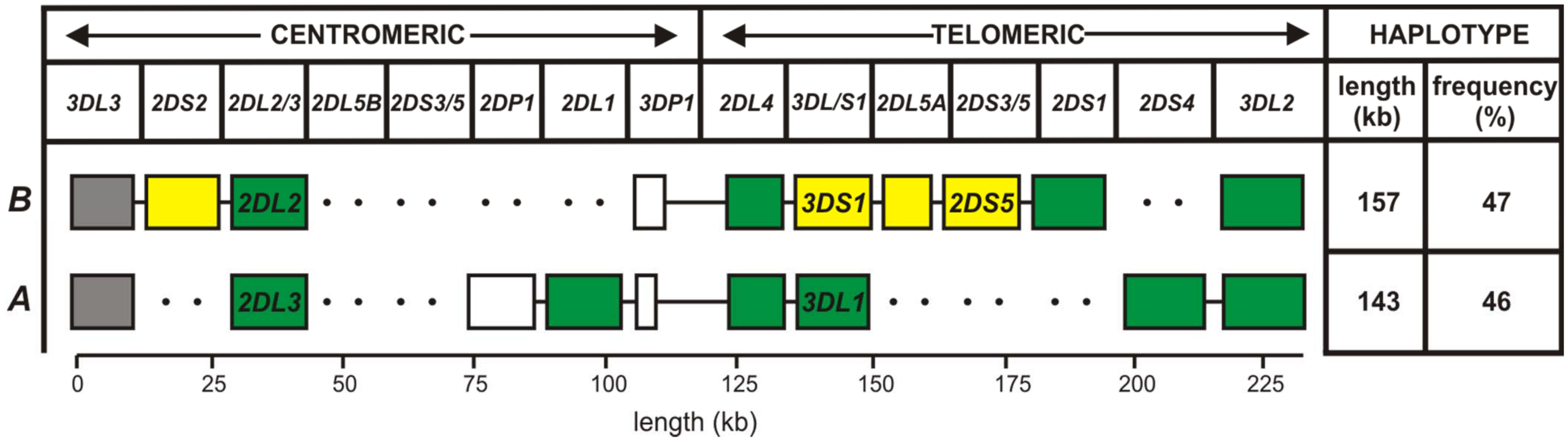
1. Yucpa have one *A* and one *B* gene-content haplotype at balanced frequency.

KIR in Yucpa Amerindians: a population surviving many episodes of epidemic disease and population bottleneck



1. Yucpa have one *A* and one *B* gene-content haplotype at balanced frequency.
2. These divergent gene content haplotypes allow Yucpa to retain all *KIR* except *KIR2DS3*.

KIR in Yucpa Amerindians: a population surviving many episodes of epidemic disease and population bottleneck



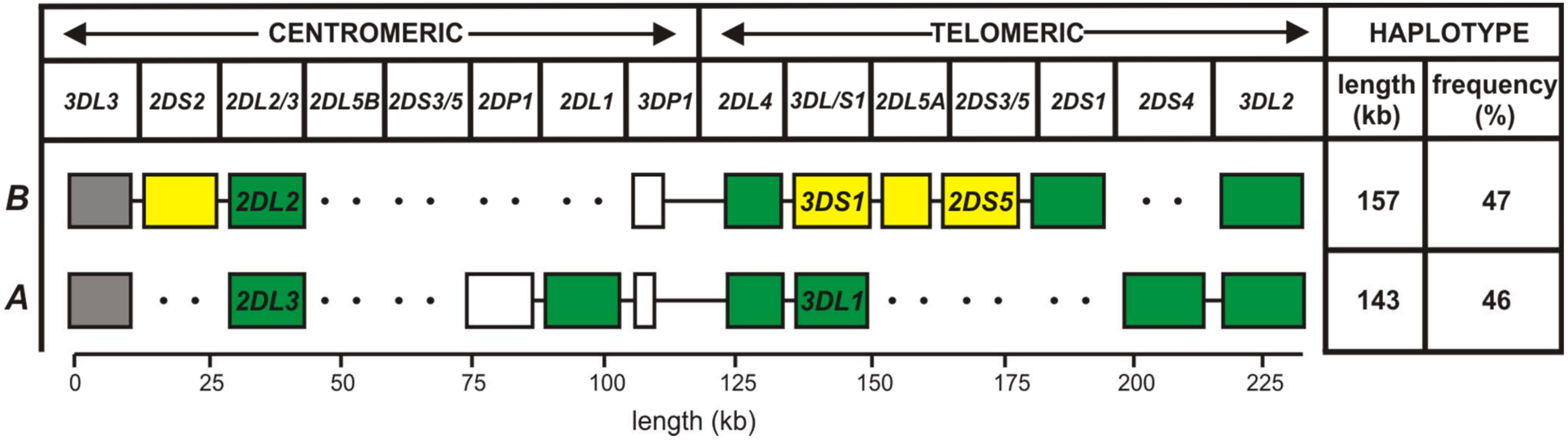
HAPLOTYPE	length (kb)	frequency (%)
B	157	47
A	143	46

1. Yucpa have one *A* and one *B* gene-content haplotype at balanced frequency.

2. These divergent gene content haplotypes allow Yucpa to retain all *KIR* except *KIR2DS3*.

3. The *A* haplotype is enriched for polymorphic inhibitory KIR that bind to HLA class 1 (green).

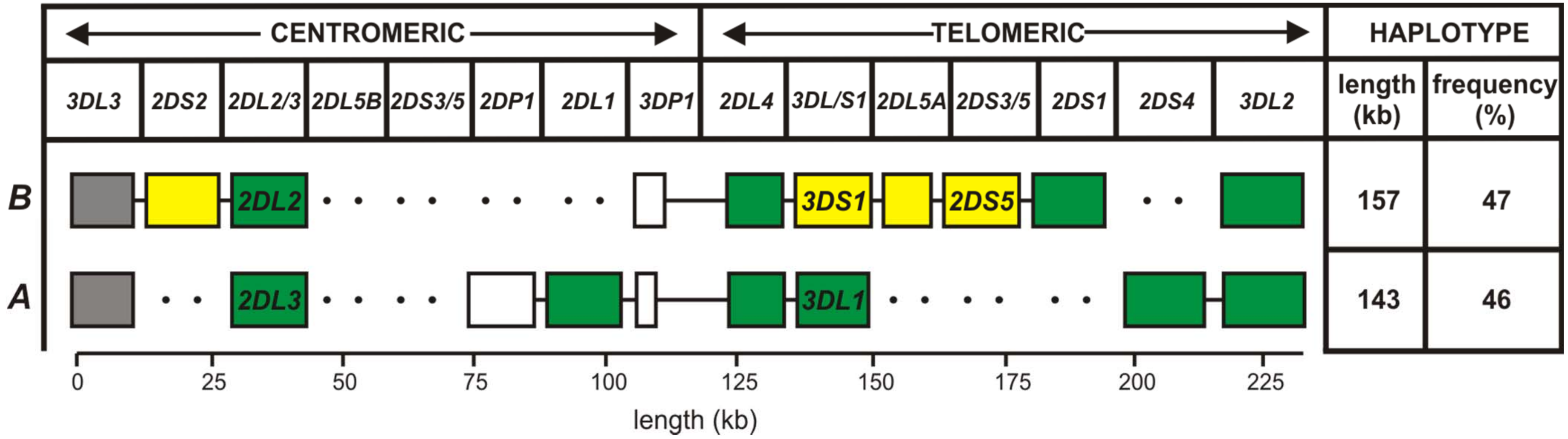
KIR in Yucpa Amerindians: a population surviving many episodes of epidemic disease and population bottleneck



HAPLOTYPE	length (kb)	frequency (%)
B	157	47
A	143	46

1. Yucpa have one *A* and one *B* gene-content haplotype at balanced frequency.
2. These divergent gene content haplotypes allow Yucpa to retain all *KIR* except *KIR2DS3*.
3. The *A* haplotype is enriched for polymorphic inhibitory KIR that bind to HLA class 1 (green).
4. The *B* haplotype is enriched for non-polymorphic attenuated KIR.

KIR in Yucpa Amerindians: a population surviving many episodes of epidemic disease and population bottleneck

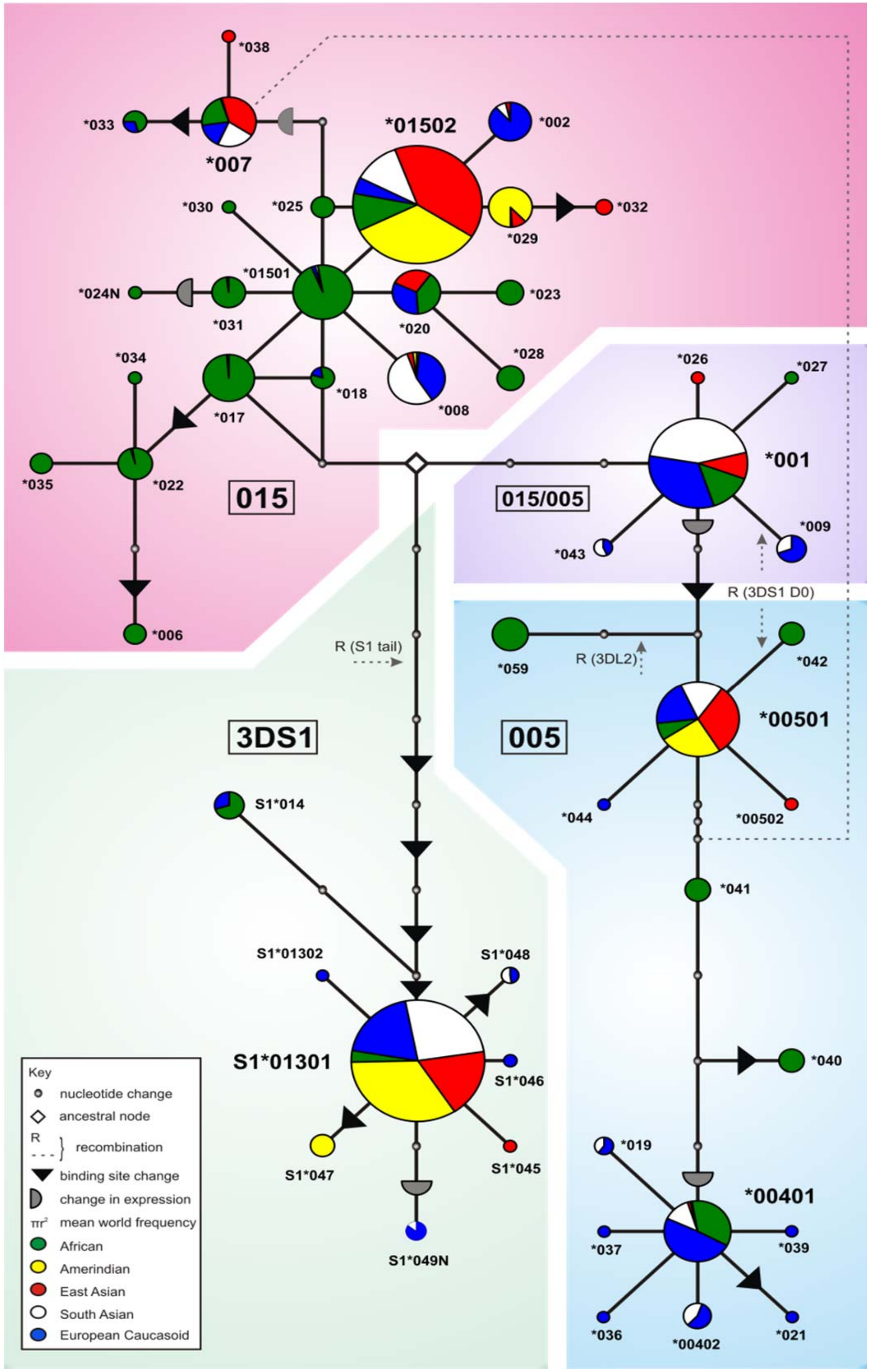


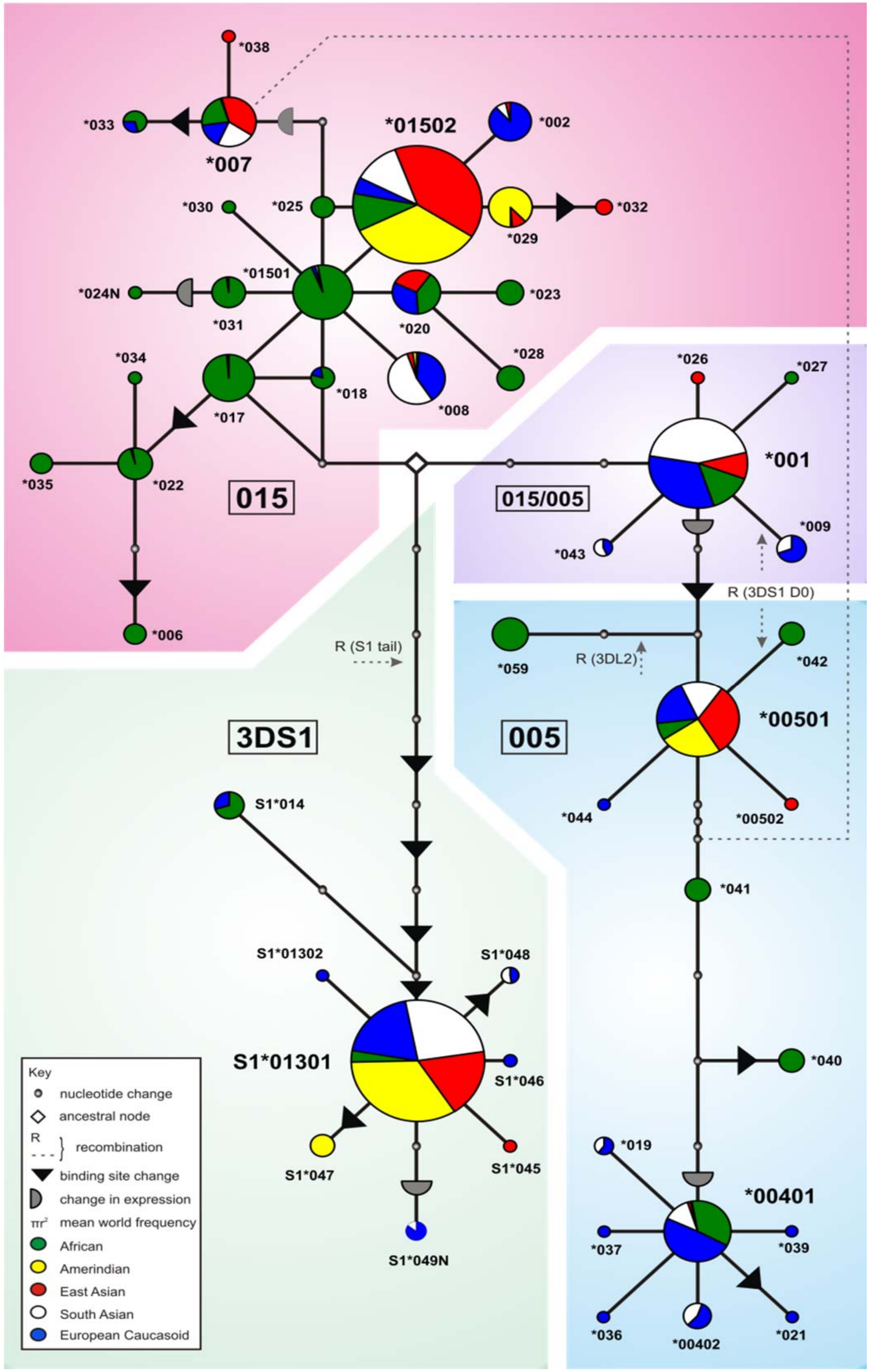
3. The *A* haplotype is enriched for polymorphic inhibitory KIR that bind to HLA class 1 (green).

4. The *B* haplotype is enriched for non-polymorphic attenuated KIR.

5. Illustrate with KIR3DL1/S1: Norman’s network.

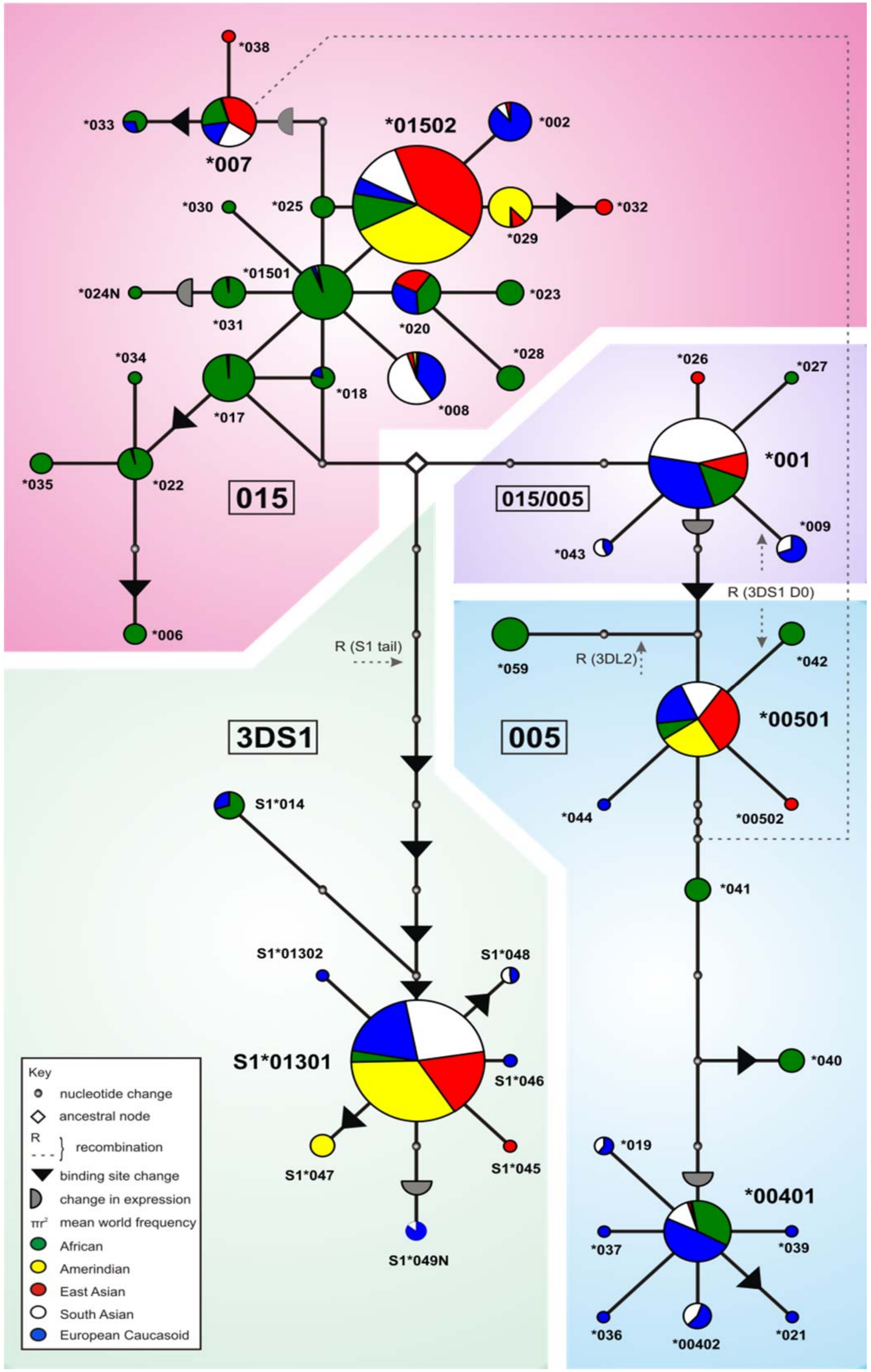
Worldwide variation in KIR3DL1/S1





Worldwide variation in KIR3DL1/S1

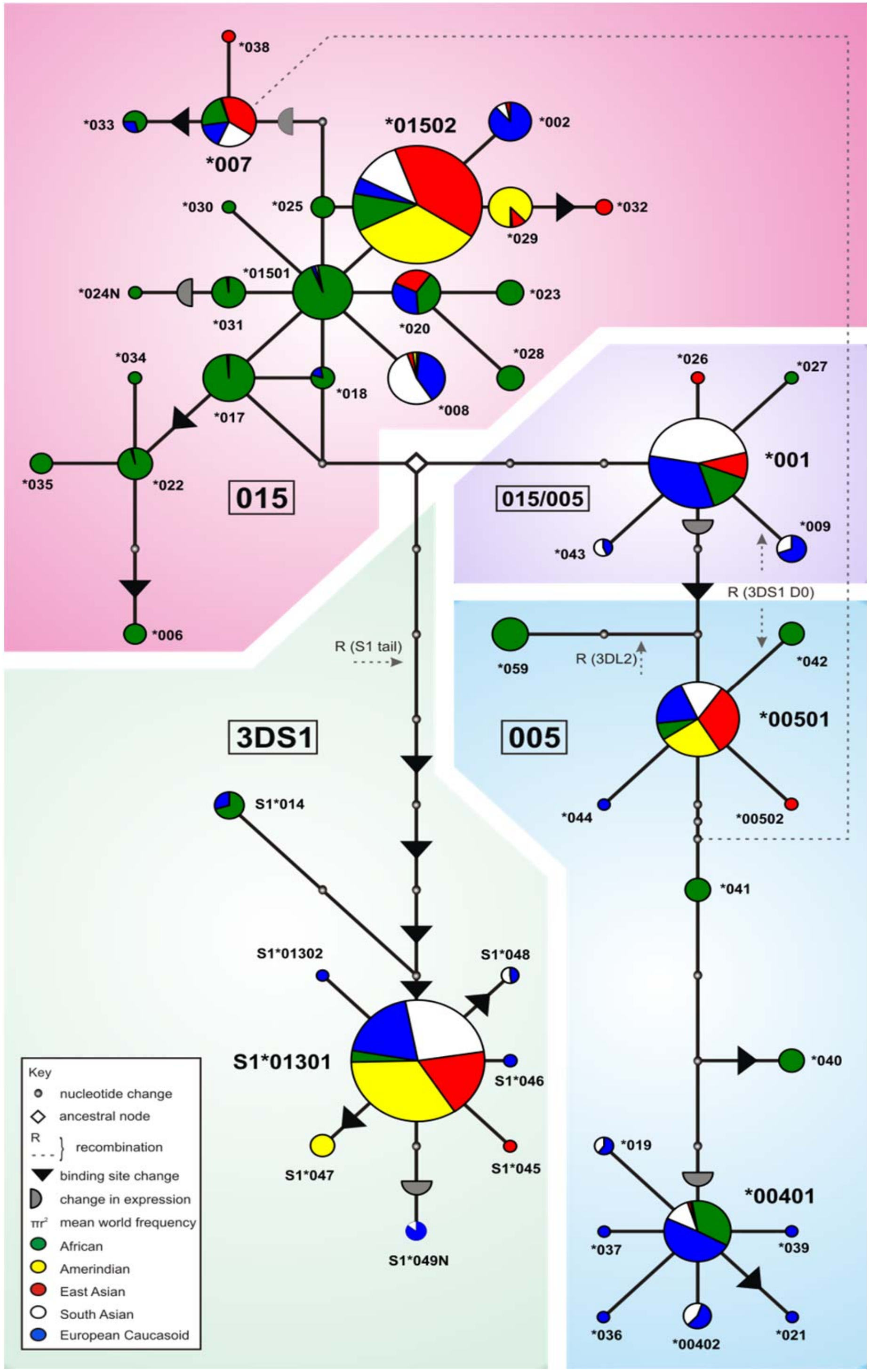
1. **Three lineages diverged ~3mya.**



Worldwide variation in KIR3DL1/S1

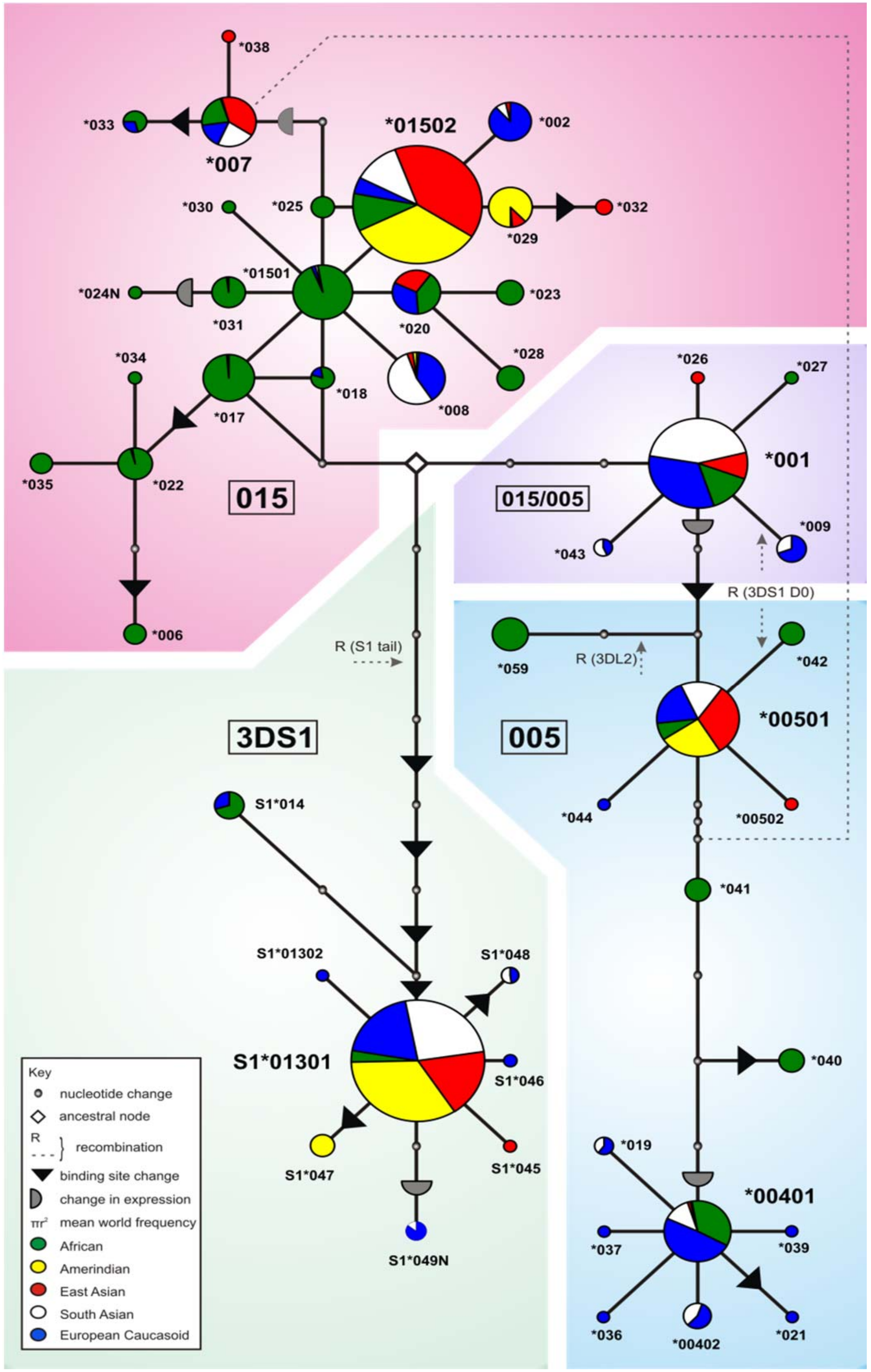
1. **Three lineages diverged ~3mya.**
2. **Subject to balancing selection.**

Worldwide variation in KIR3DL1/S1



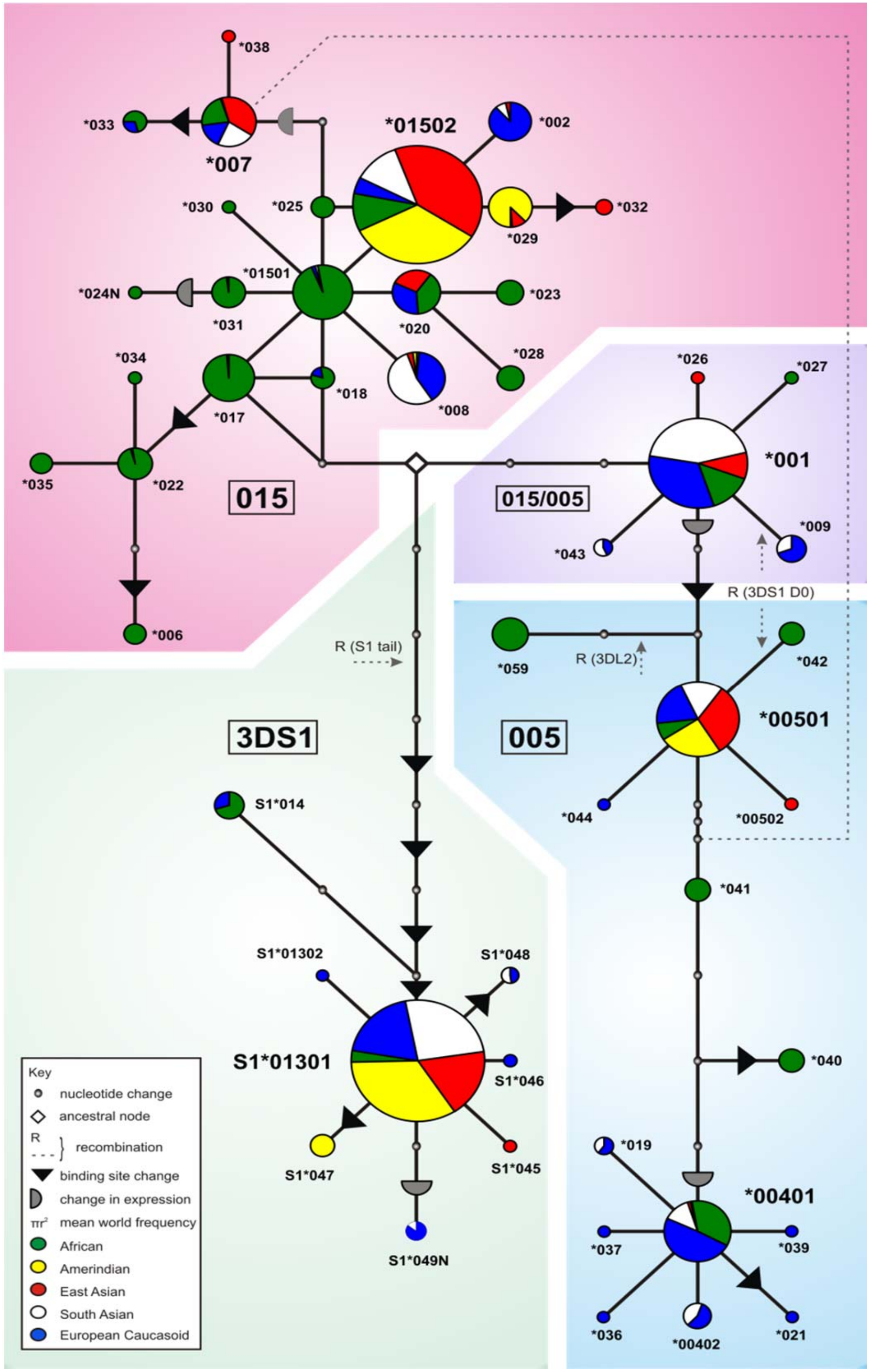
1. **Three lineages diverged ~3mya.**
2. **Subject to balancing selection.**
3. **Represented in all populations, but the balance varies.**

Worldwide variation in KIR3DL1/S1



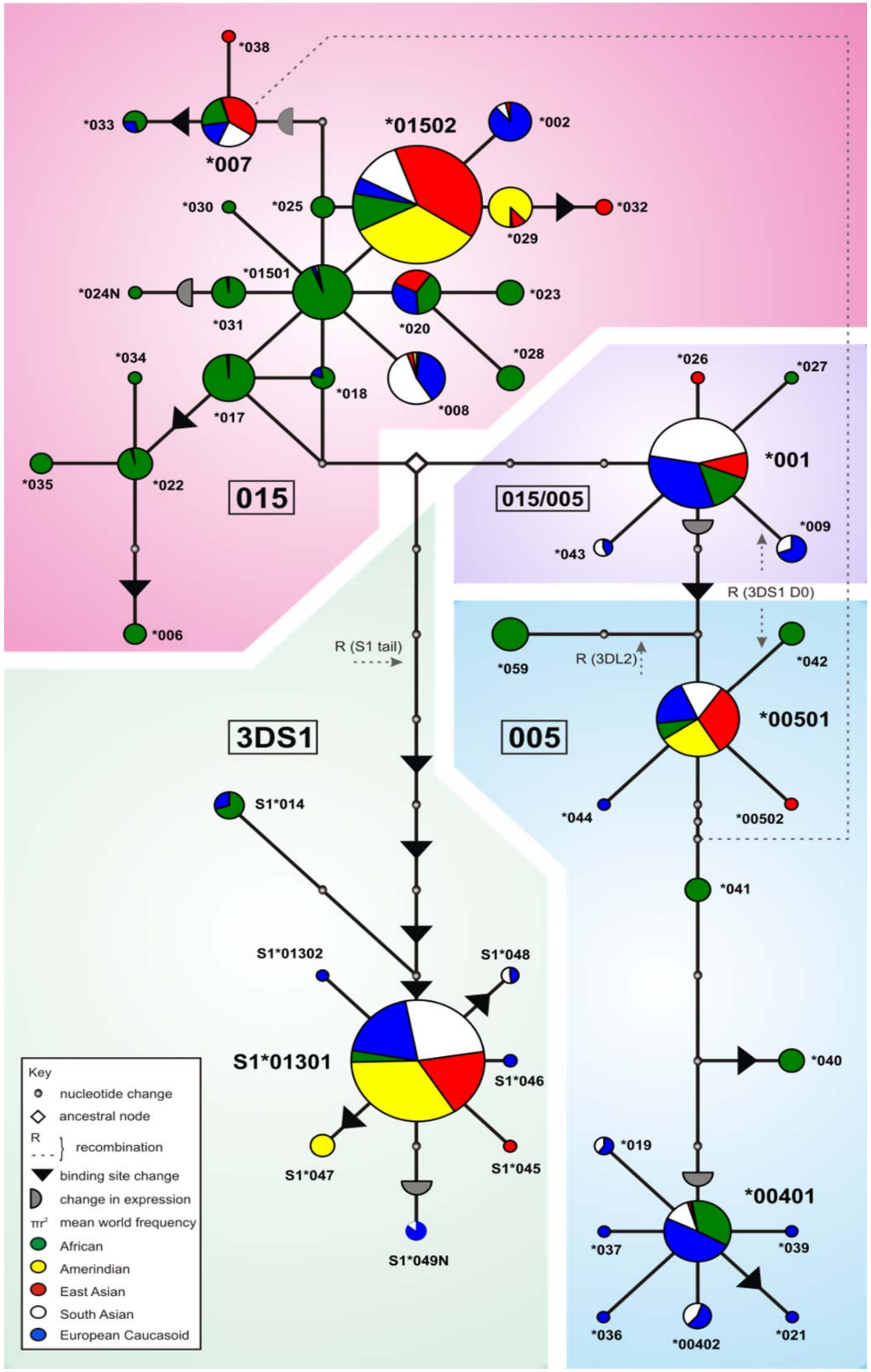
1. **Three lineages diverged ~3mya.**
2. **Subject to balancing selection.**
3. **Represented in all populations, but the balance varies.**
4. **3DL1 is polymorphic, 3DS1 is conserved**

Worldwide variation in KIR3DL1/S1



1. Three lineages diverged ~3mya.
2. Subject to balancing selection.
3. Represented in all populations, but the balance varies.
4. 3DL1 is polymorphic, 3DS1 is conserved
5. 3DL1 binds Bw4 epitope well, 3DS1 does not bind HLA at all.

Worldwide variation in KIR3DL1/S1



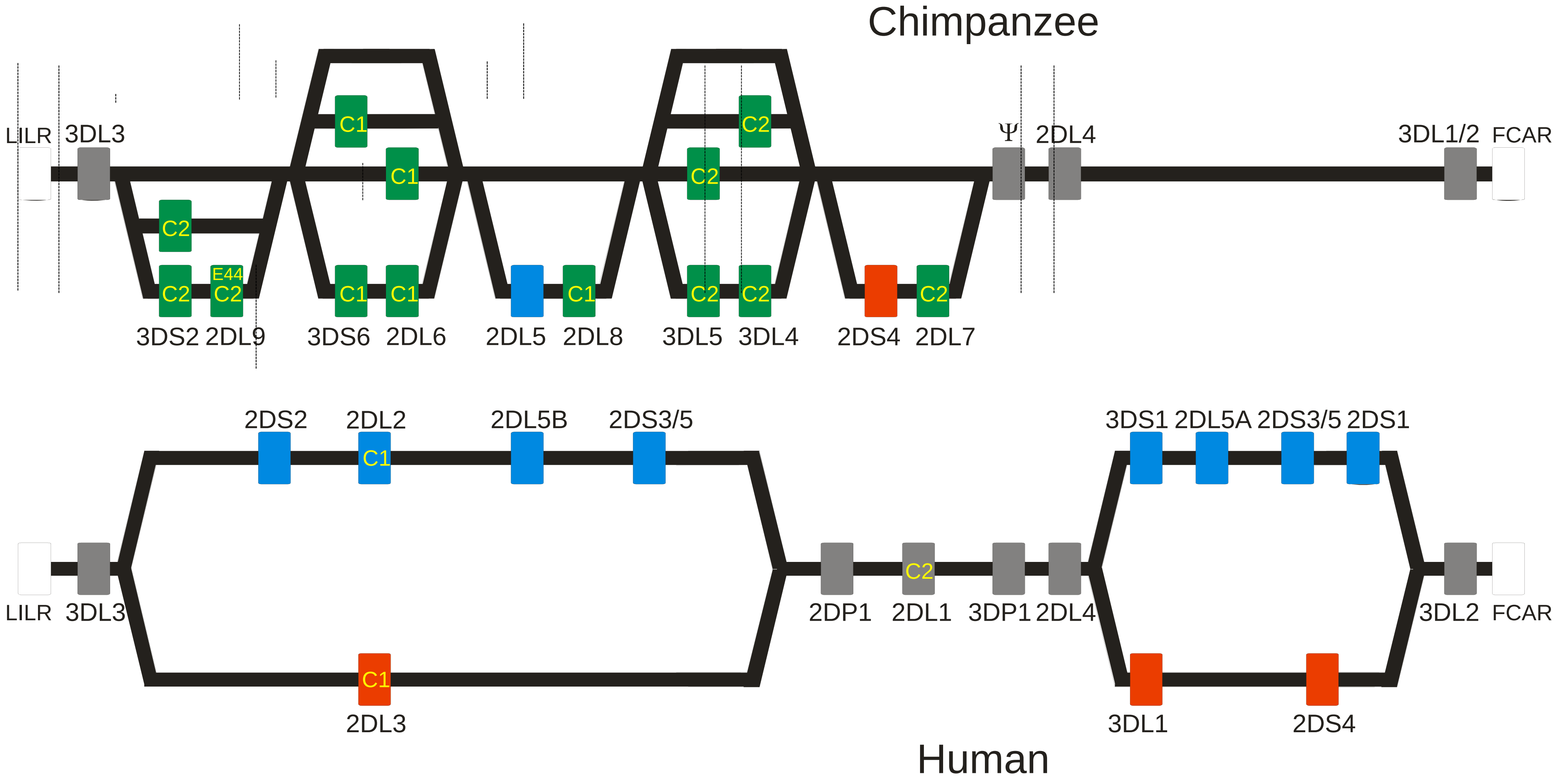
1. Three lineages diverged ~3mya.
2. Subject to balancing selection.
3. Represented in all populations, but the balance varies.
4. 3DL1 is polymorphic, 3DS1 is conserved
5. 3DL1 binds Bw4 epitope well, 3DS1 does not bind HLA at all.
6. 3DS1*013 is the most abundant form of KIR3DL1/S1.

Chimpanzees are our closest living relatives.

What do their *KIR* haplotypes look like?

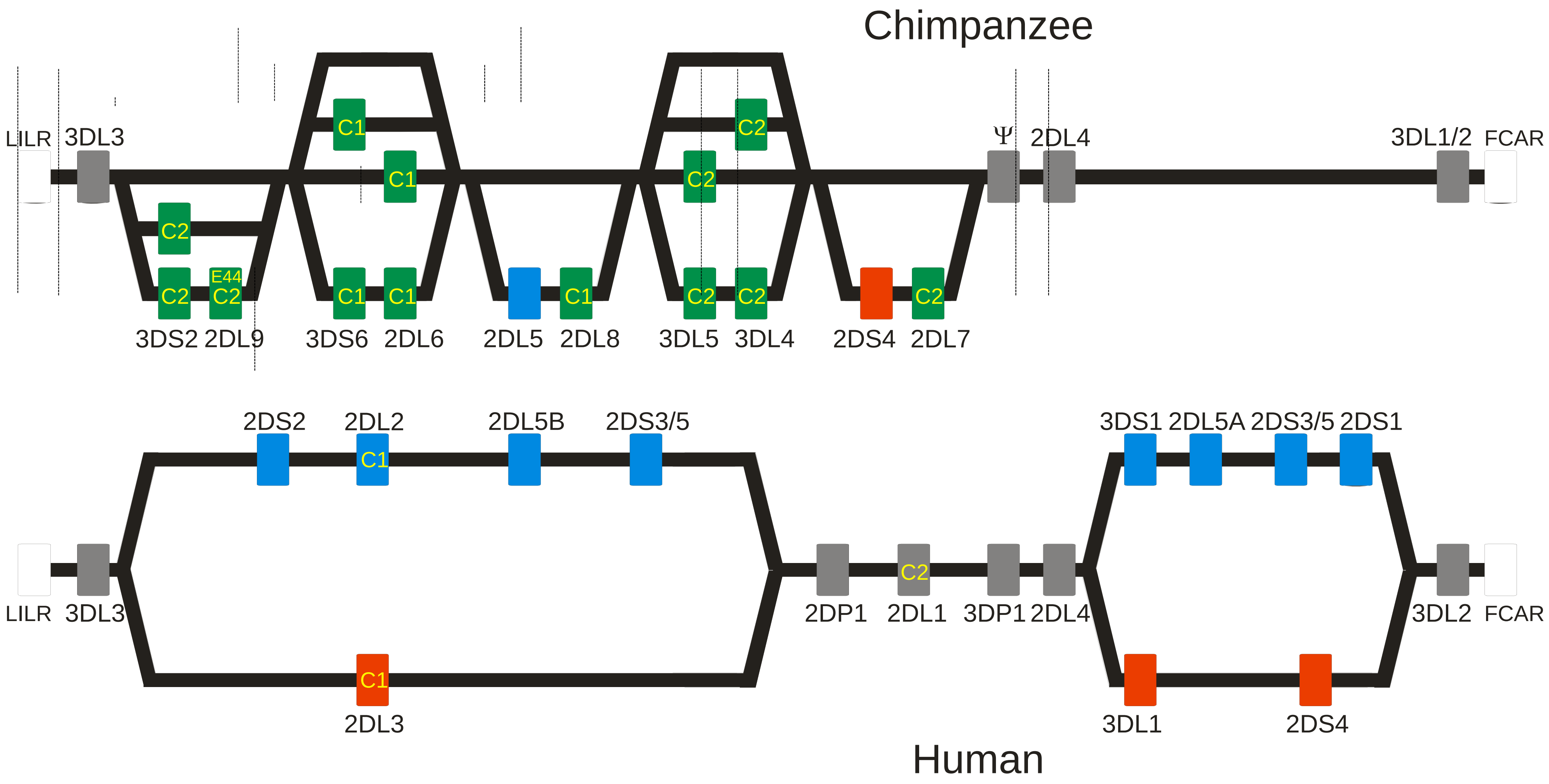
Do they have *A* and *B* *KIR* haplotypes like us?

Chimpanzee *KIR* haplotypes form a single group more like the human *A KIR* haplotypes



Abi-Rached et al 2010, PLoS Genetics

Human-specific evolution of *A* and *B KIR* haplotypes through reorganising the locus and selecting for qualitatively and quantitatively different types of *KIR*



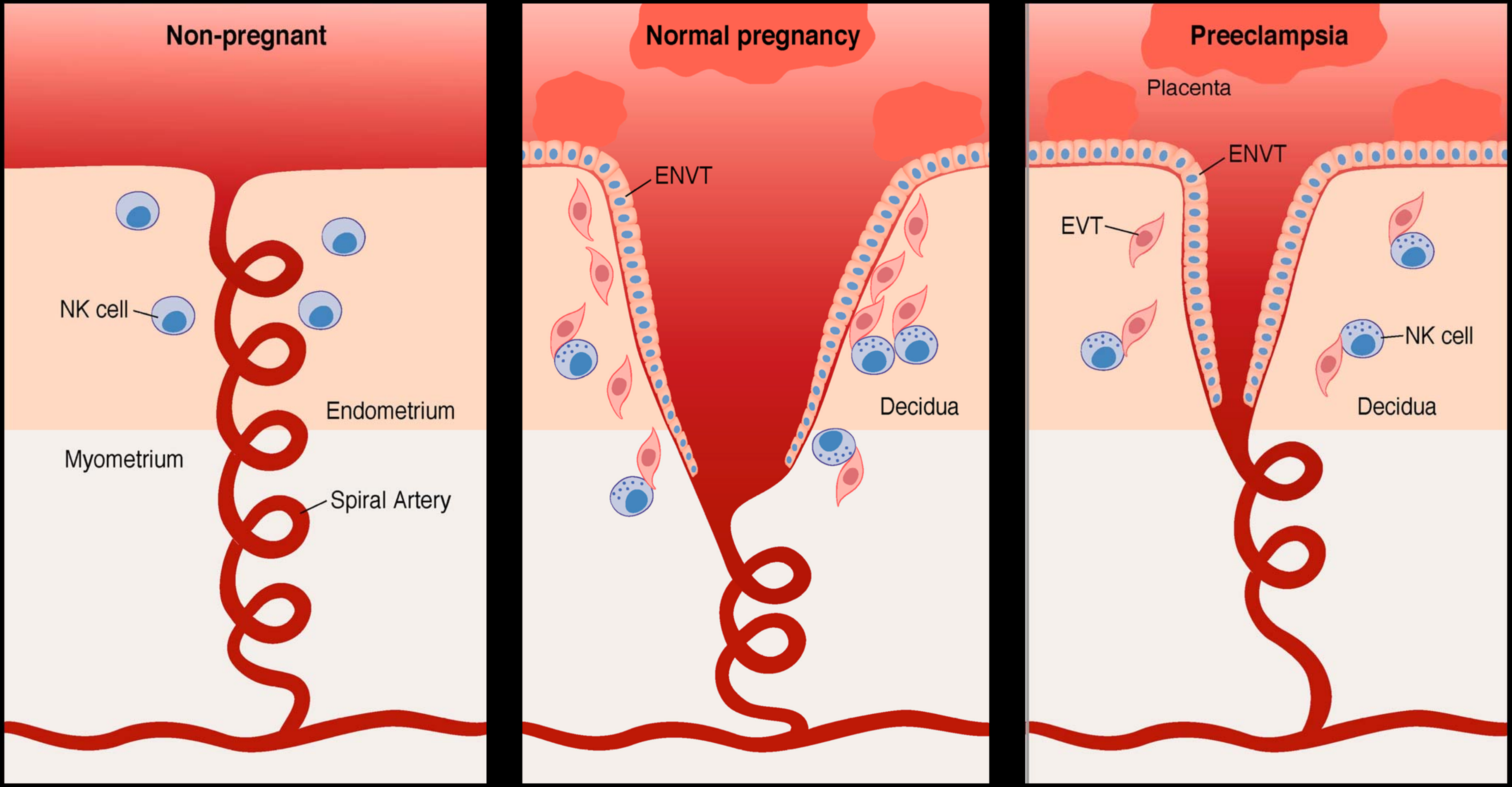
Abi-Rached et al 2010, PLoS Genetics

The Extraordinary Immunogenetics of Natural Killer (NK) Cell Receptors and Major Histocompatibility Complex (MHC) Class I Ligands

[3] Human-specific evolution of variable NK cell receptors.

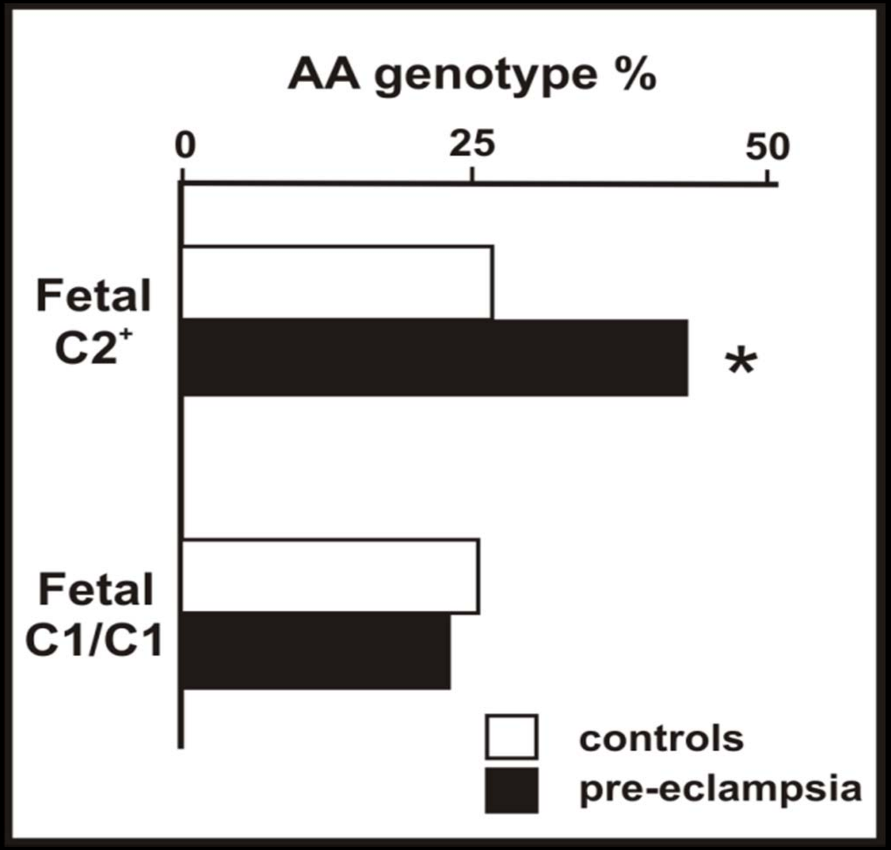
Compound genotype of HLA class I and KIR are associated with various infectious and reproductive diseases.

Preeclampsia and other pregnancy disorders correlate with insufficient remodeling of the spiral arteries



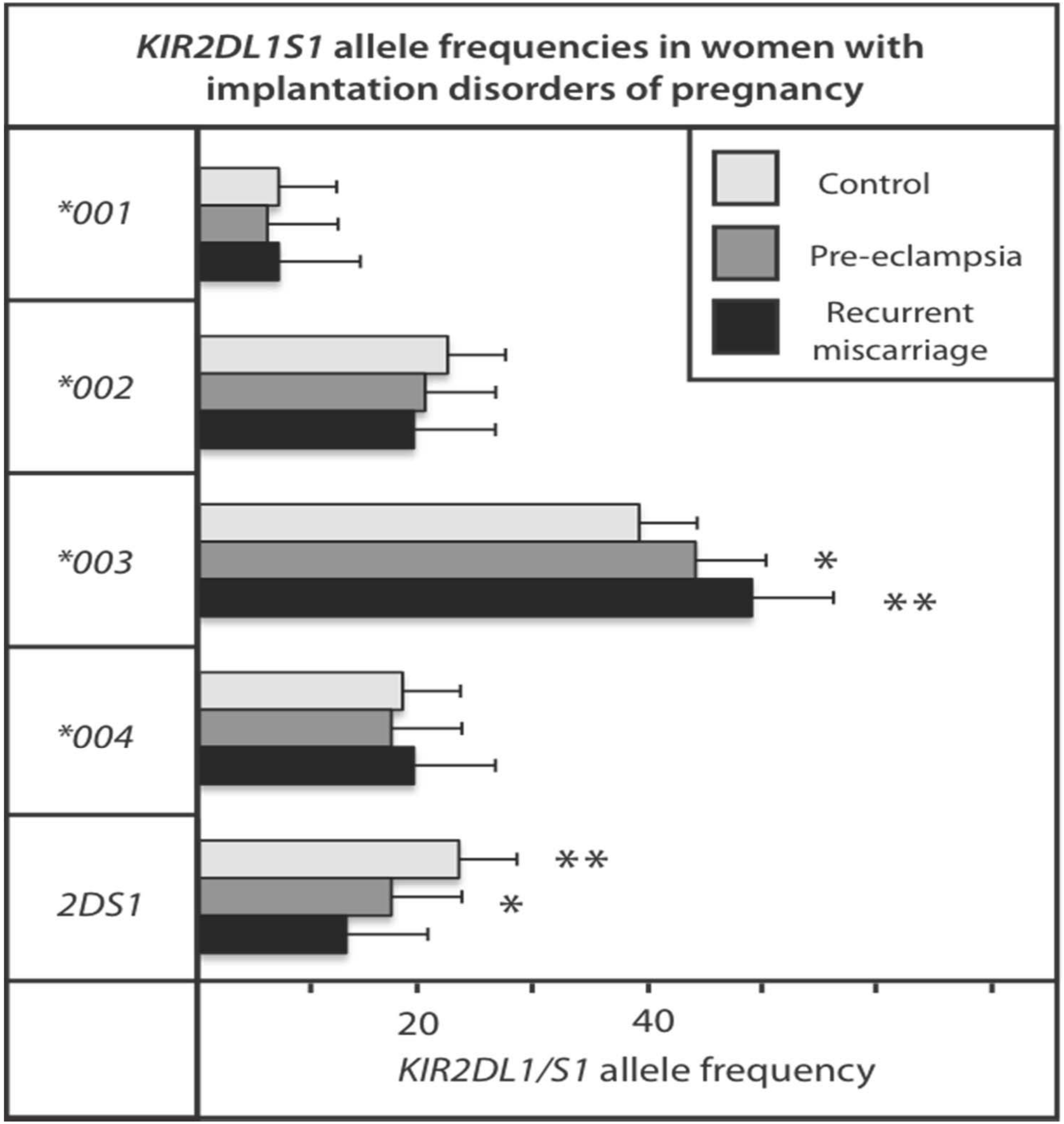
Diseases Associated With Group *A* and *B KIR* Haplotypes

Reproductive disorder: pre-eclampsia



B haplotype good, A haplotype bad

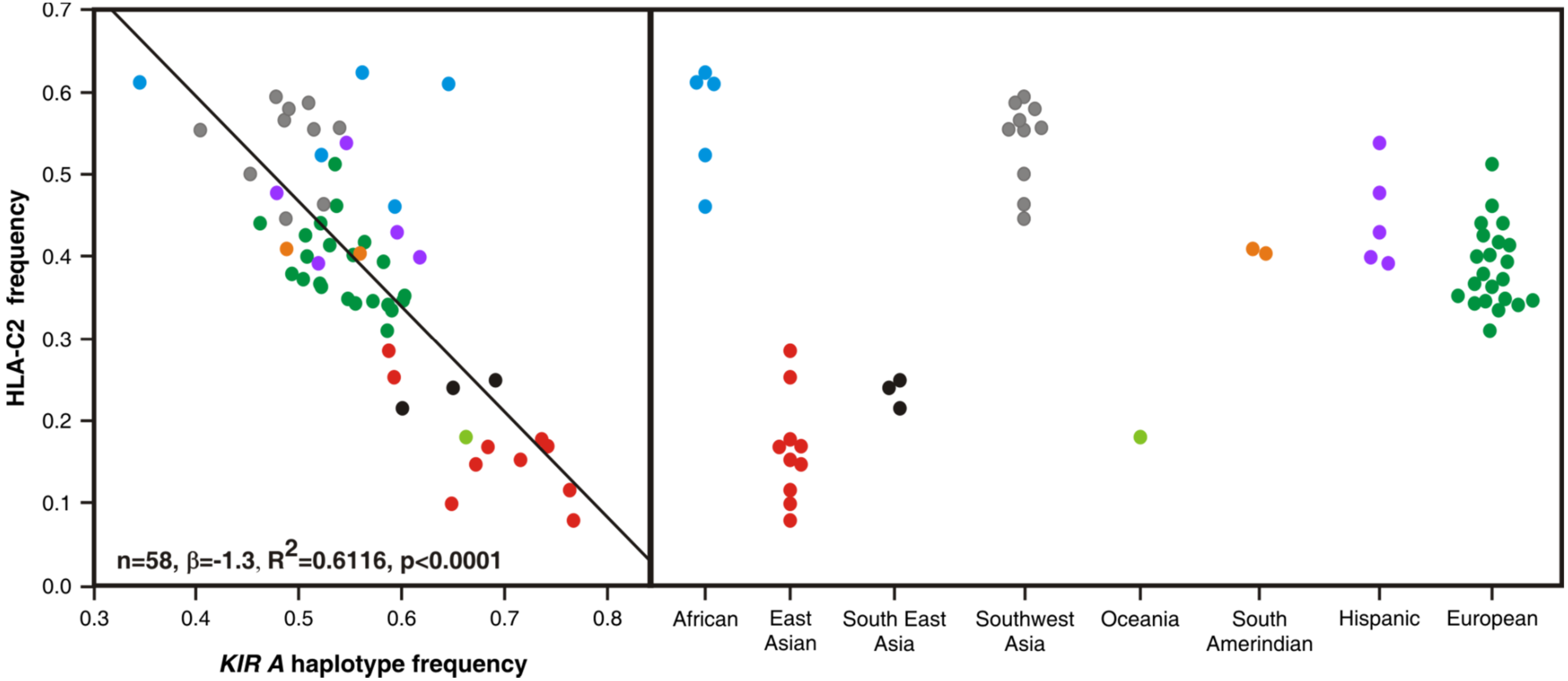
Hiby et al: J Exp Med 2004, JCI 2010



Collaboration with Ashley Moffett

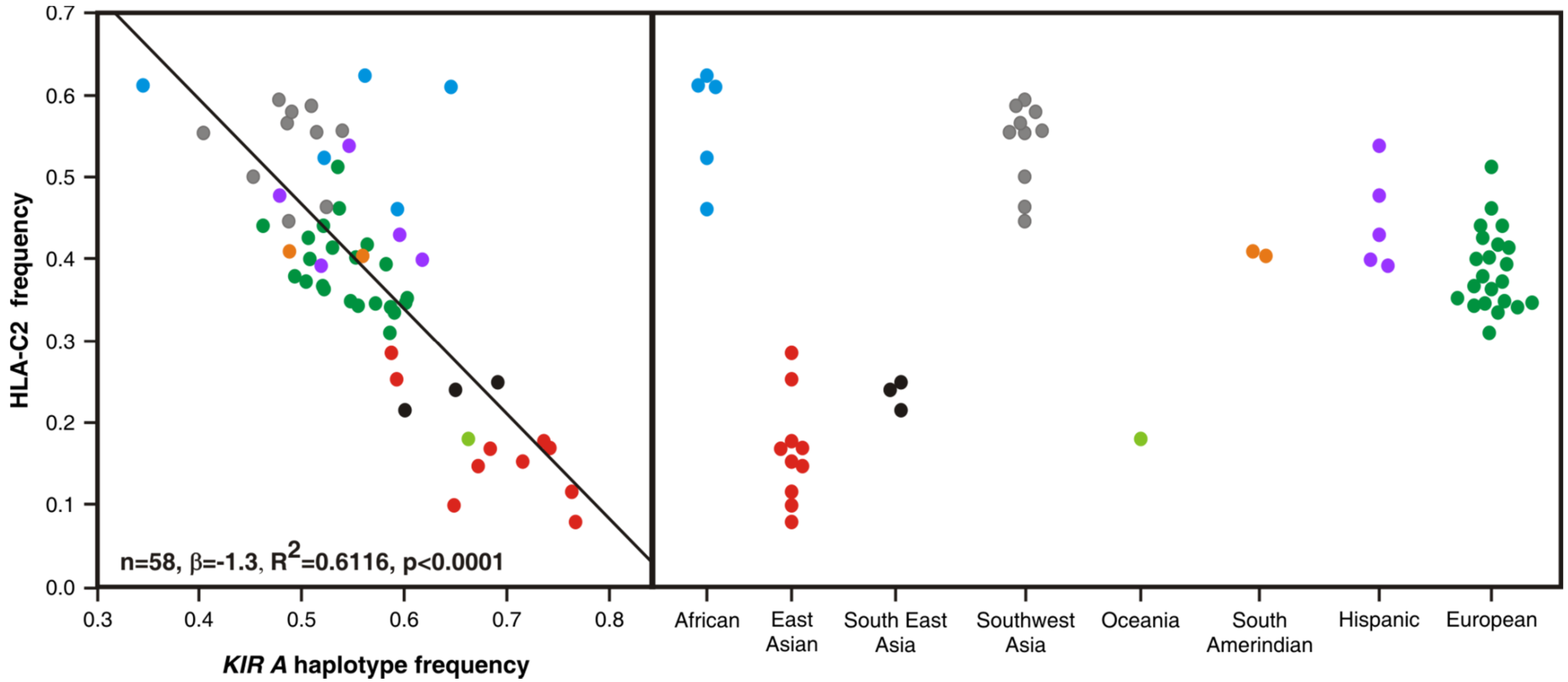
Inhibitory KIR2DL1*003 confers risk,activating KIR2DS1*002 protects.

Today's human populations carry a strong genetic imprint from past selection by pregnancy disorder



Extending Hiby et al 2004, JEM.

Today's Human Populations Carry The Strong Genetic Imprint from Past Selection by Pregnancy Disorder



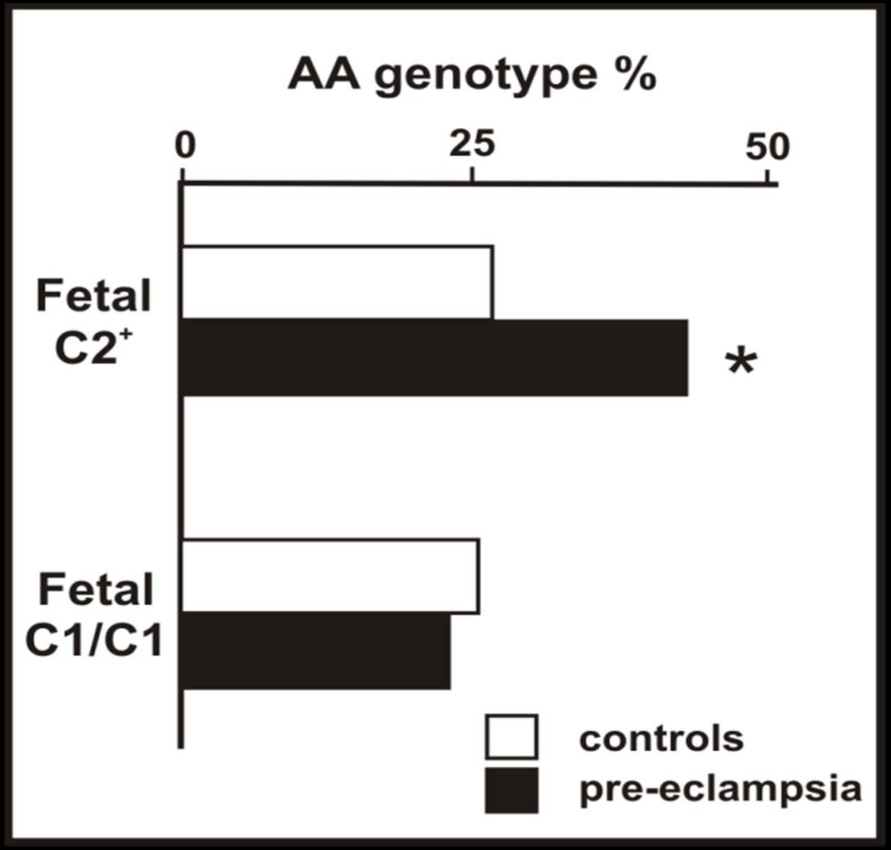
Recurrent abortion: prevents reproduction

Pre-eclampsia/ eclampsia: kills mother and child

Fetal growth restriction: produces less viable/competitive offspring

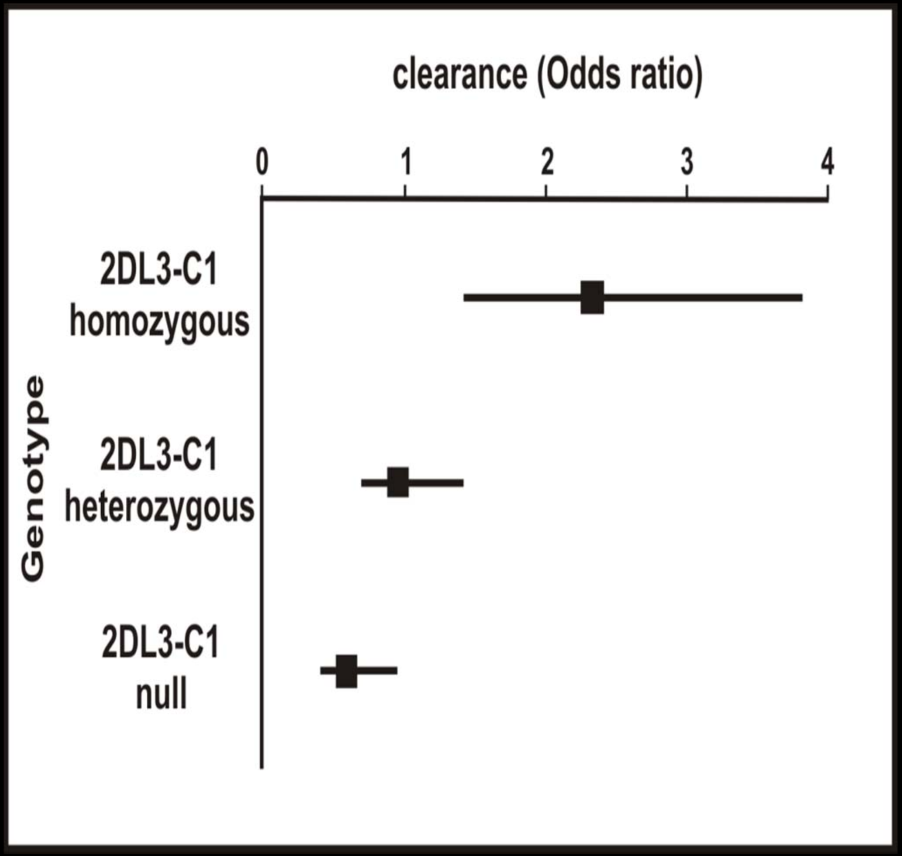
Diseases Associated With Group *A* and *B* *KIR* Haplotypes

Reproductive disorder: pre-eclampsia



B haplotype good, A haplotype bad

Infectious disease: hepatitis C virus

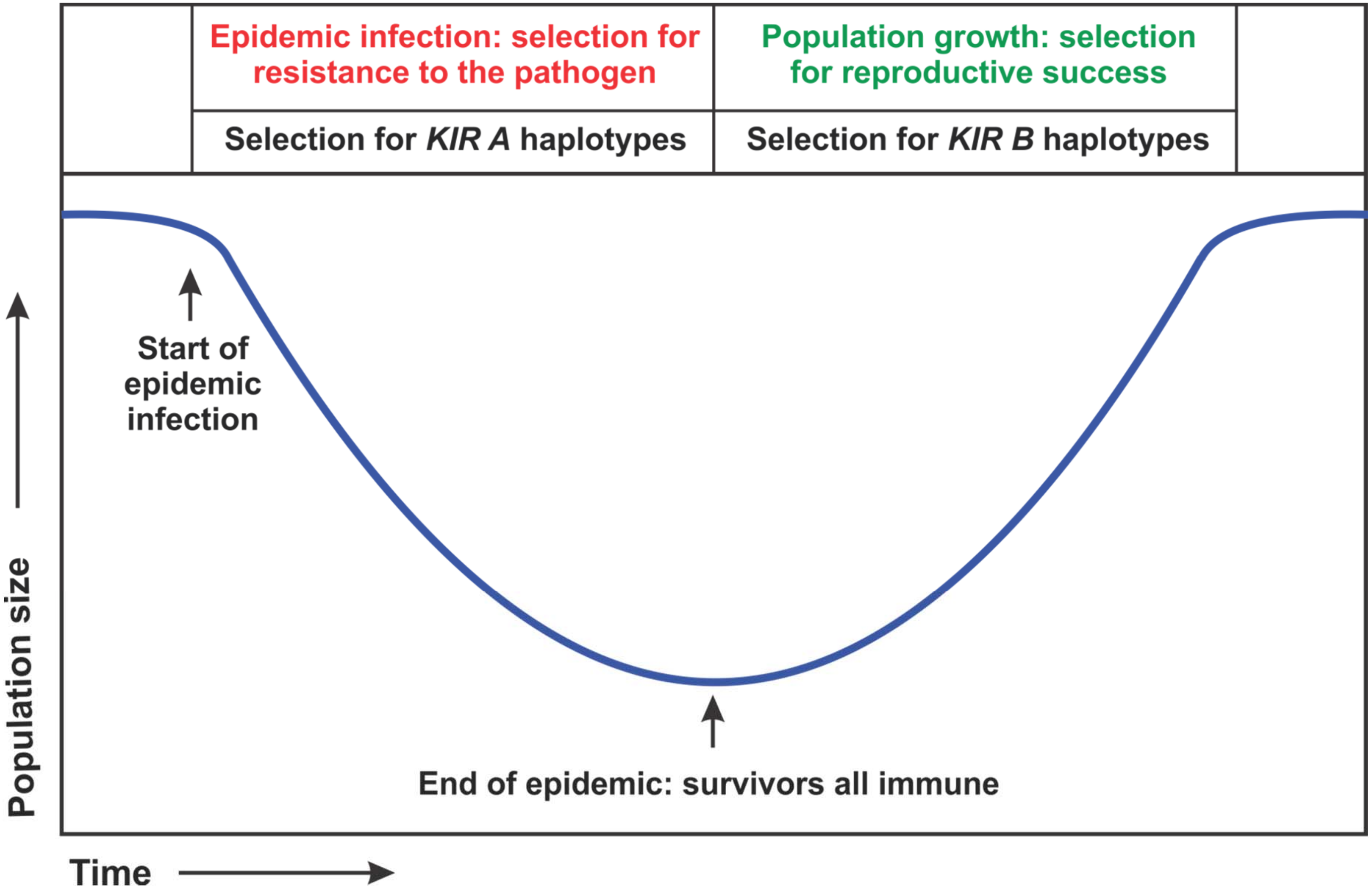


B haplotype bad, A haplotype good

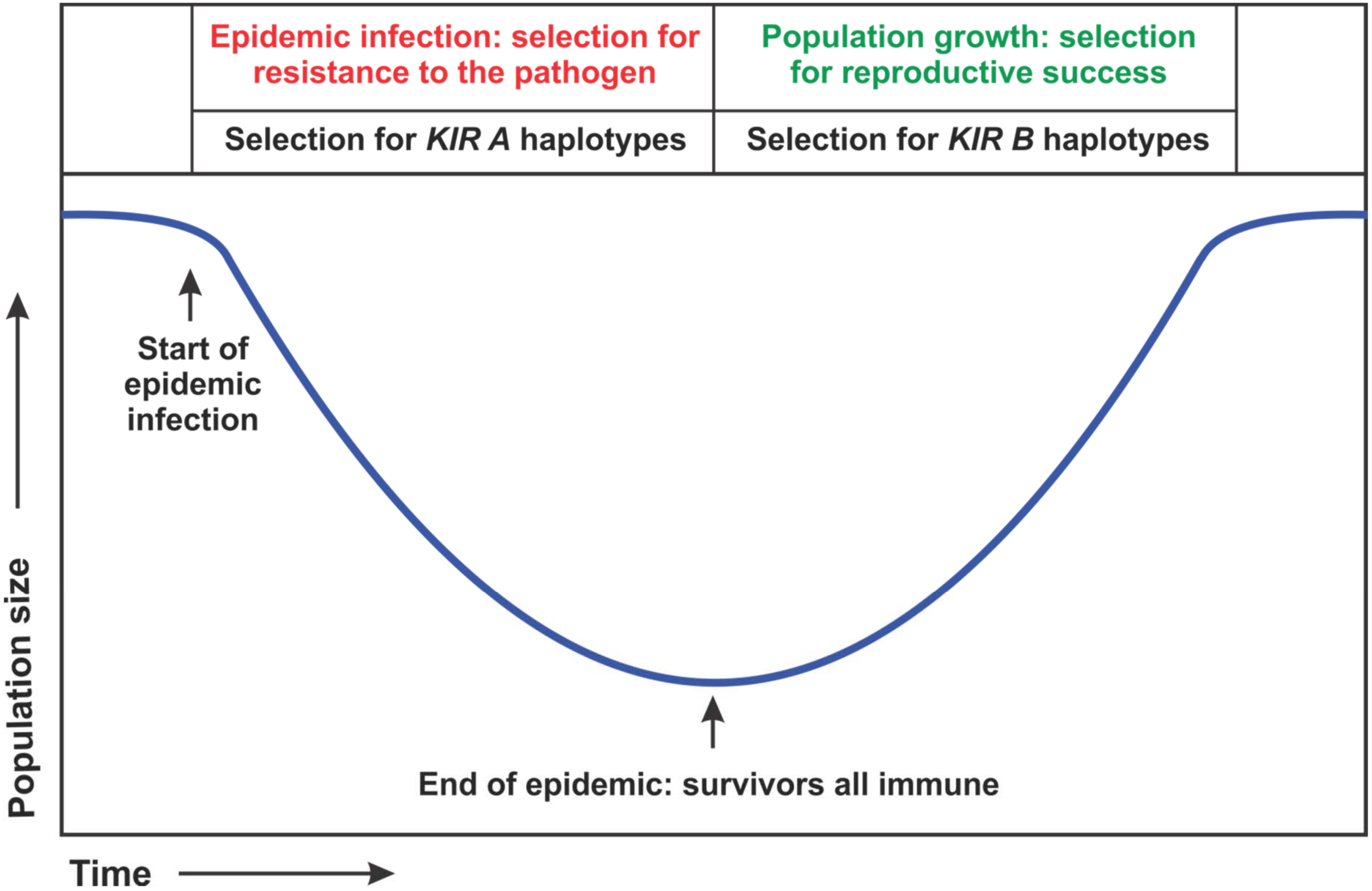
Hiby et al: J Exp Med 2004, JCI 2010

Khakoo, Carrington et al: Science 2004

Cyclical model of the human compromise in which *A* and *B* haplotypes are subject to balancing selection imposed by the competing needs of immune defense and reproduction



Cyclical model of the human compromise in which *A* and *B* haplotypes are subject to balancing selection imposed by the competing needs of immune defense and reproduction

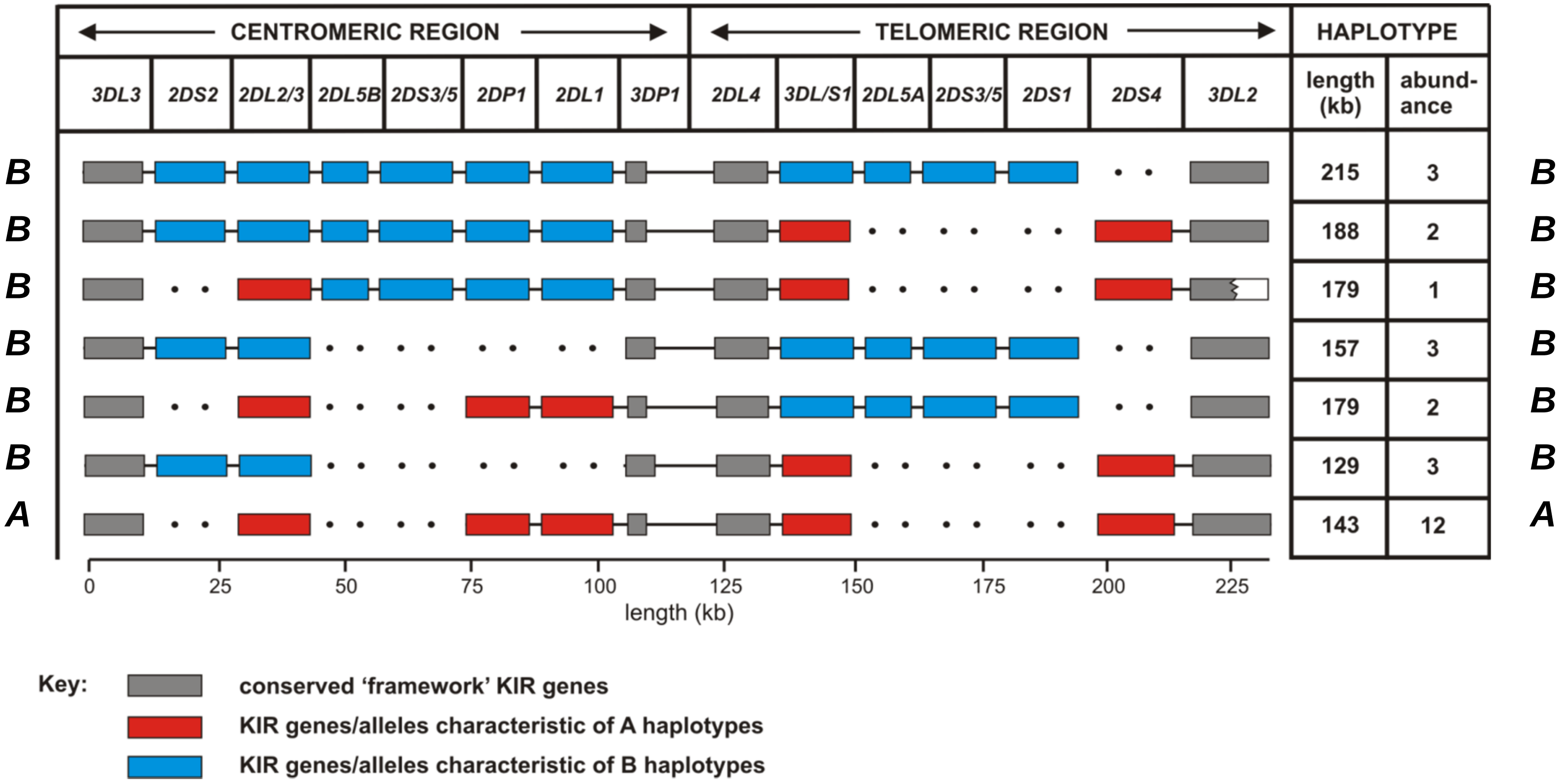


All human populations have *A* and *B KIR* haplotypes

[Q1] Why did chimpanzees not have follow an evolutionary where the KIR system was forced to make a compromise in serving the needs of immunity and reproduction?

[Q2] When was this compromise made?

Centromeric
B segment
Evolved ~5mya



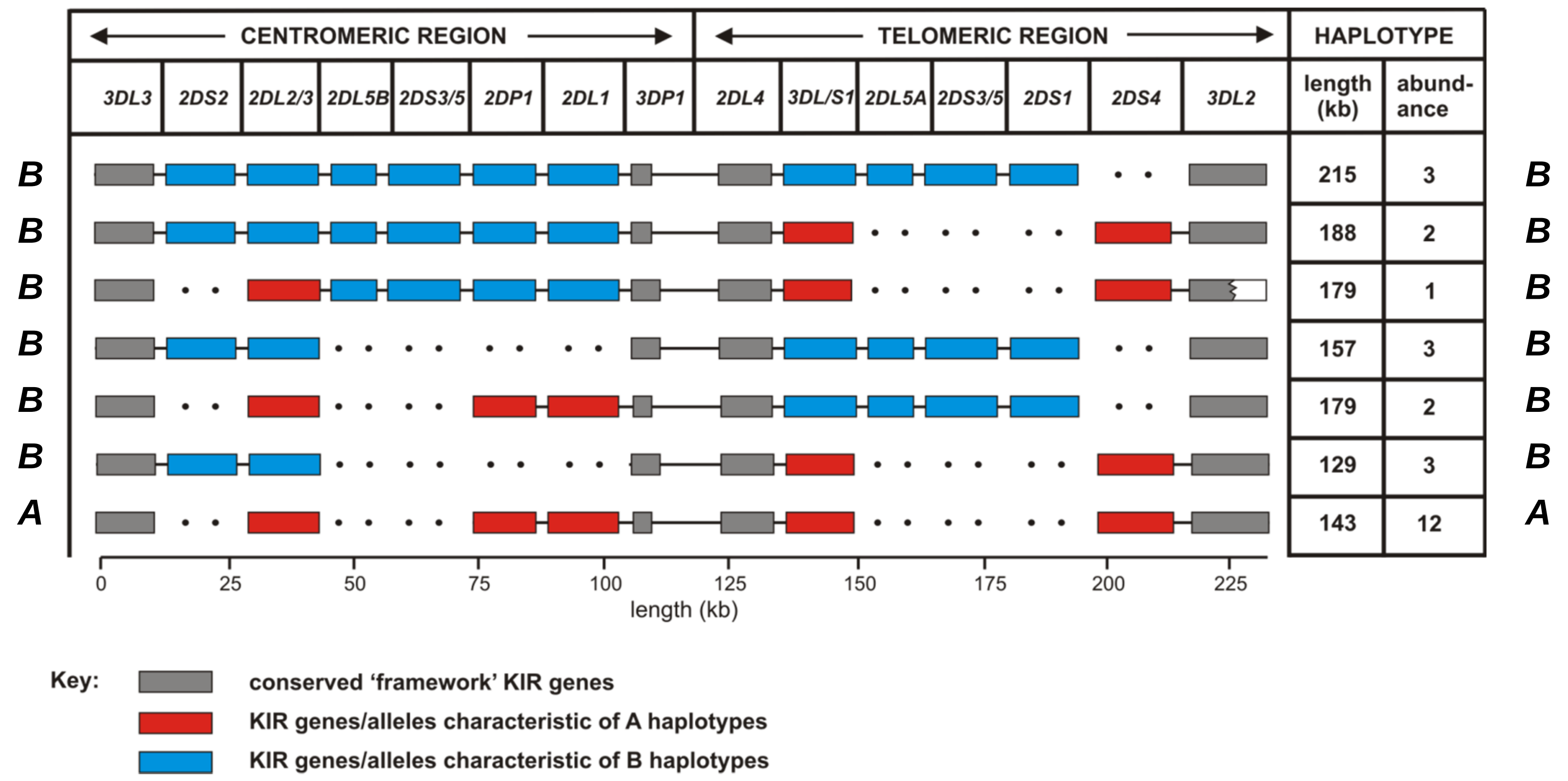
	length (kb)	abund- ance	
B	215	3	B
B	188	2	B
B	179	1	B
B	157	3	B
B	179	2	B
B	129	3	B
A	143	12	A

Sequential human-specific evolution of Centromeric B and Telomeric B gene-content motifs

Pyo, Guethlein et al PLoS One 2011

Centromeric
B segment
Evolved ~5mya

Telomeric
B segment
Evolved ~1.7mya

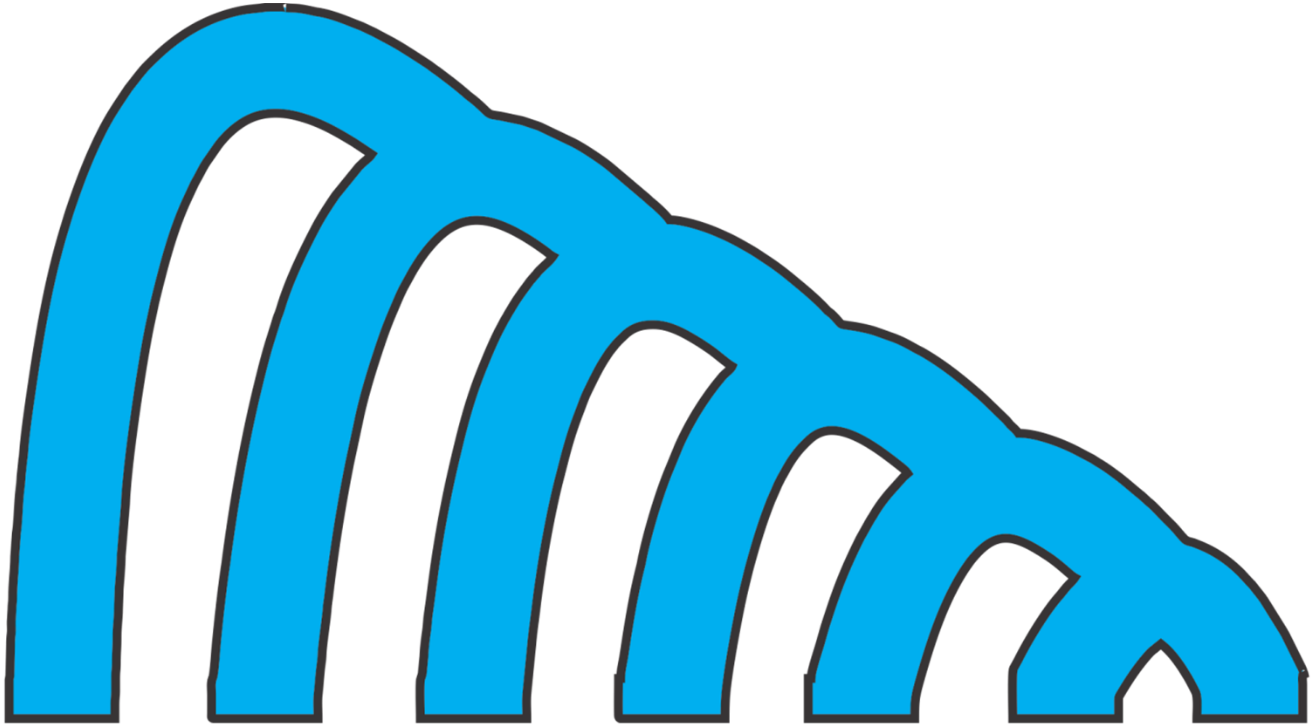


Sequential human-specific evolution of Centromeric B and Telomeric B gene-content motifs

Pyo, Guethlein et al PLoS One 2011

[Q1] Why did chimpanzees not have to follow an evolutionary trajectory where the KIR system was forced to make a compromise in serving the needs of immunity and reproduction?

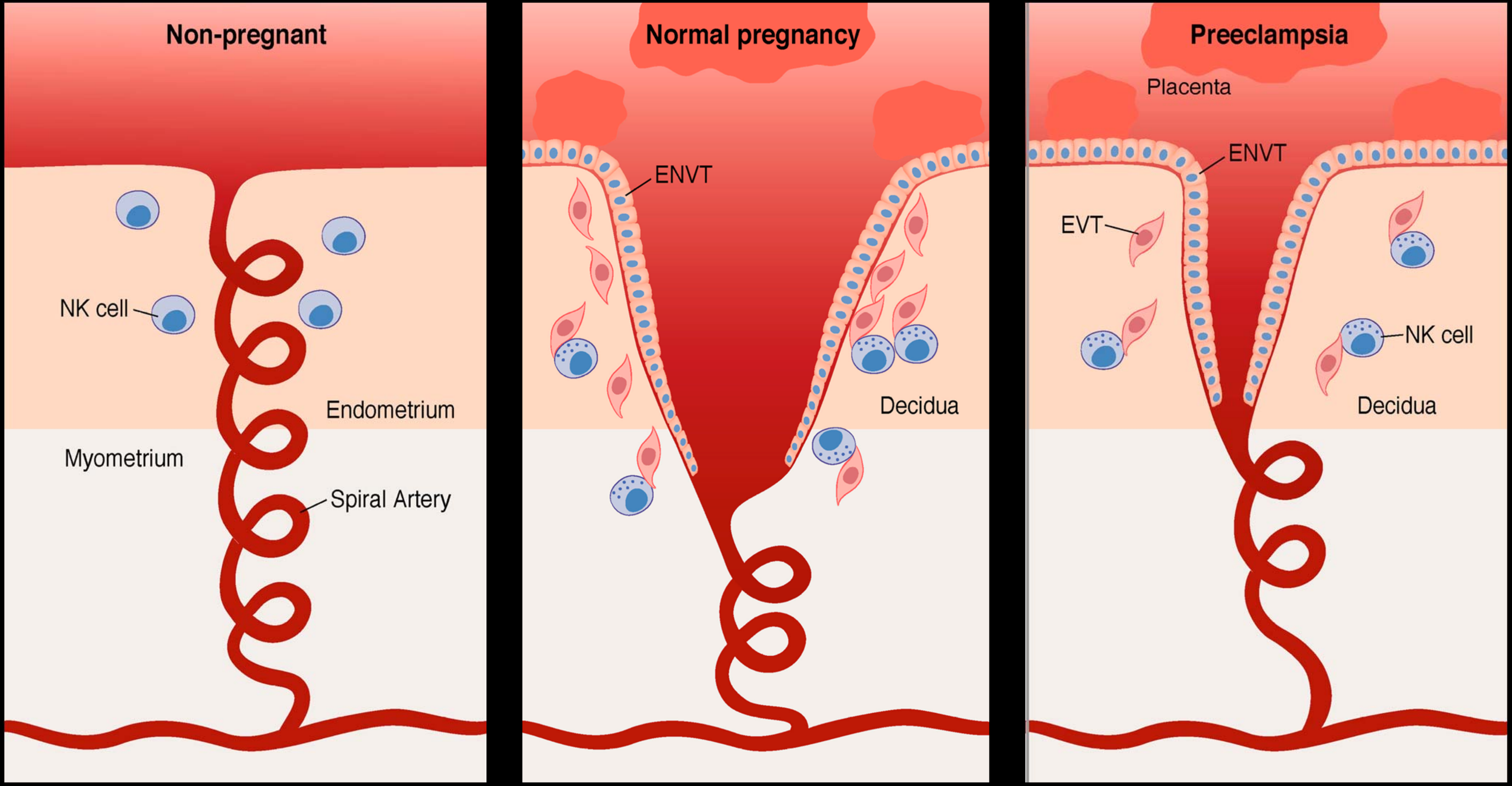
What Caused the Compromise? - Humans have much bigger brains than Chimpanzees and other Simian Primates?

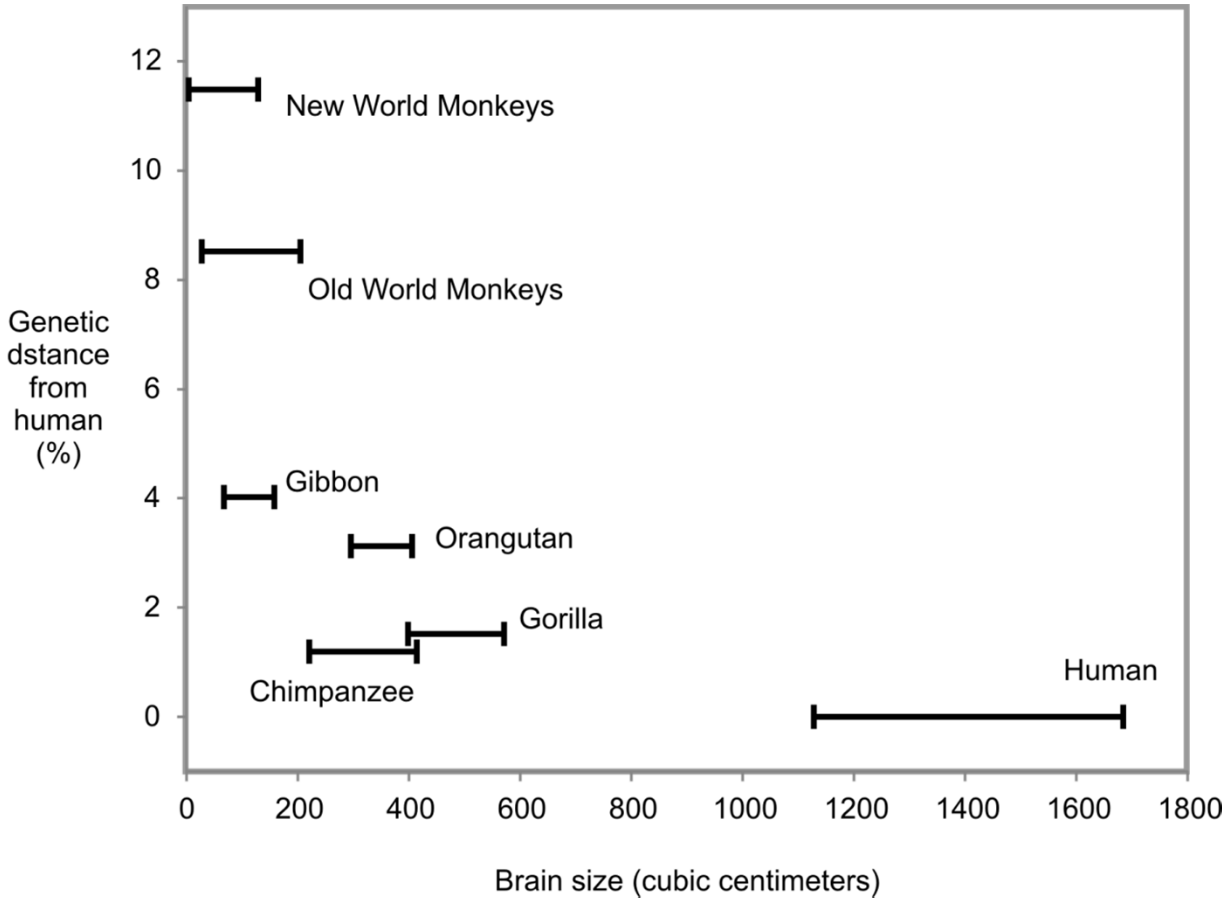


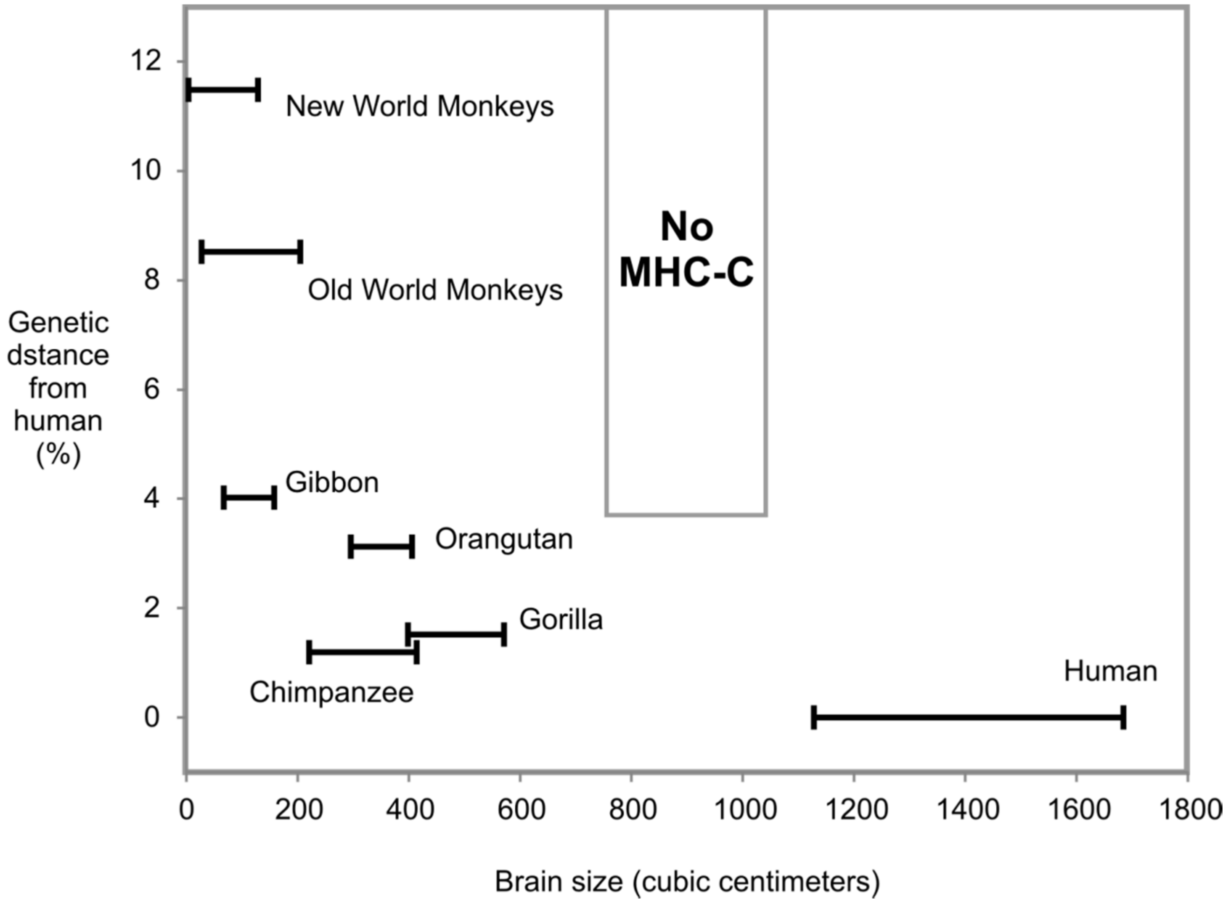
	New World Monkeys	Old World Monkeys	Gibbon	Orangutan	Gorilla	Chimpanzee	Human
Time since last common ancestor with humans (MYA)	35-40	~25	~18	~14	7-9	5-7	-
Genetic difference from human	~11.5%	~8.5%	~4.0%	~3.1%	~1.5%	~1.2%	-
Brain size (cm^3)	4-123	33-205	70-152	300-400	400-565	230-415	1129-1685

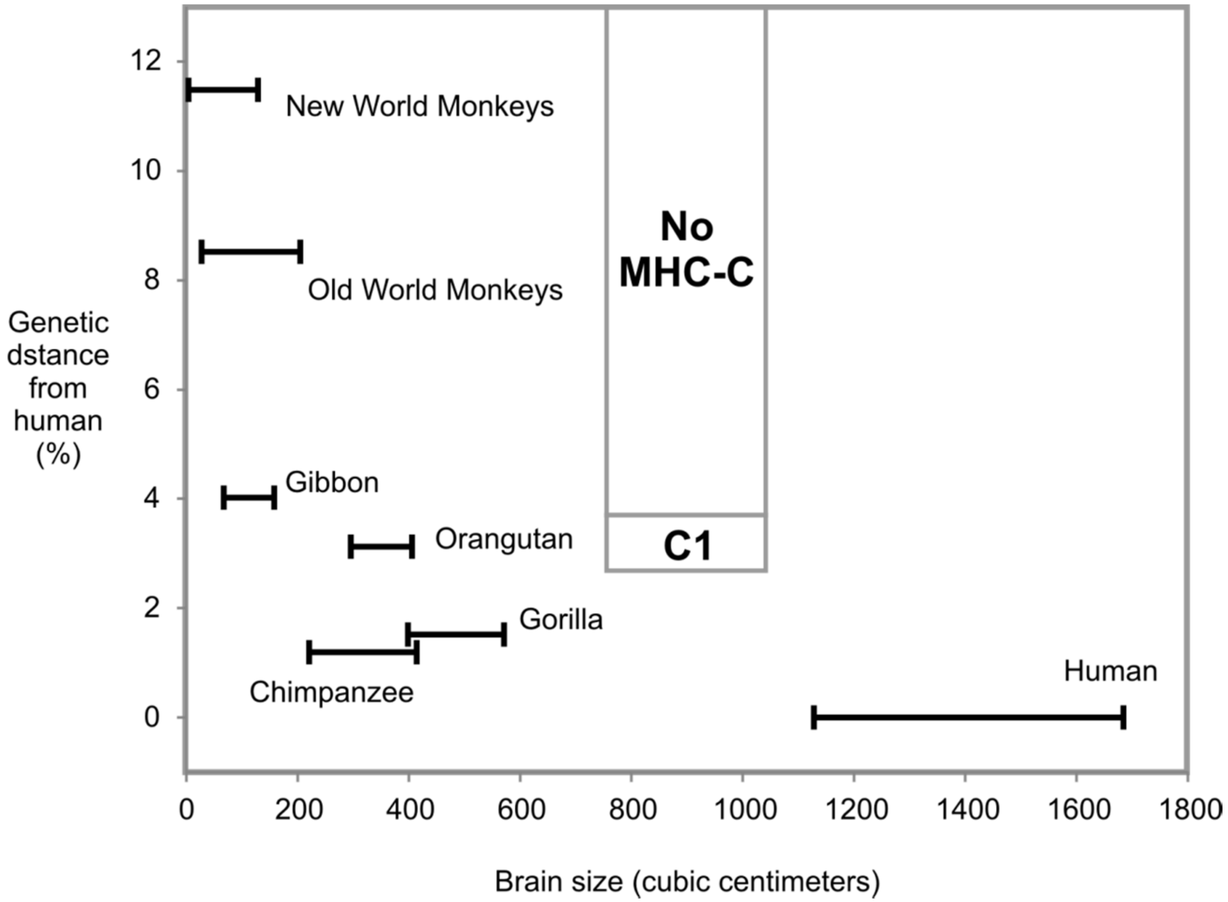
From Vallender et al 2008 Trends in Neurosciences

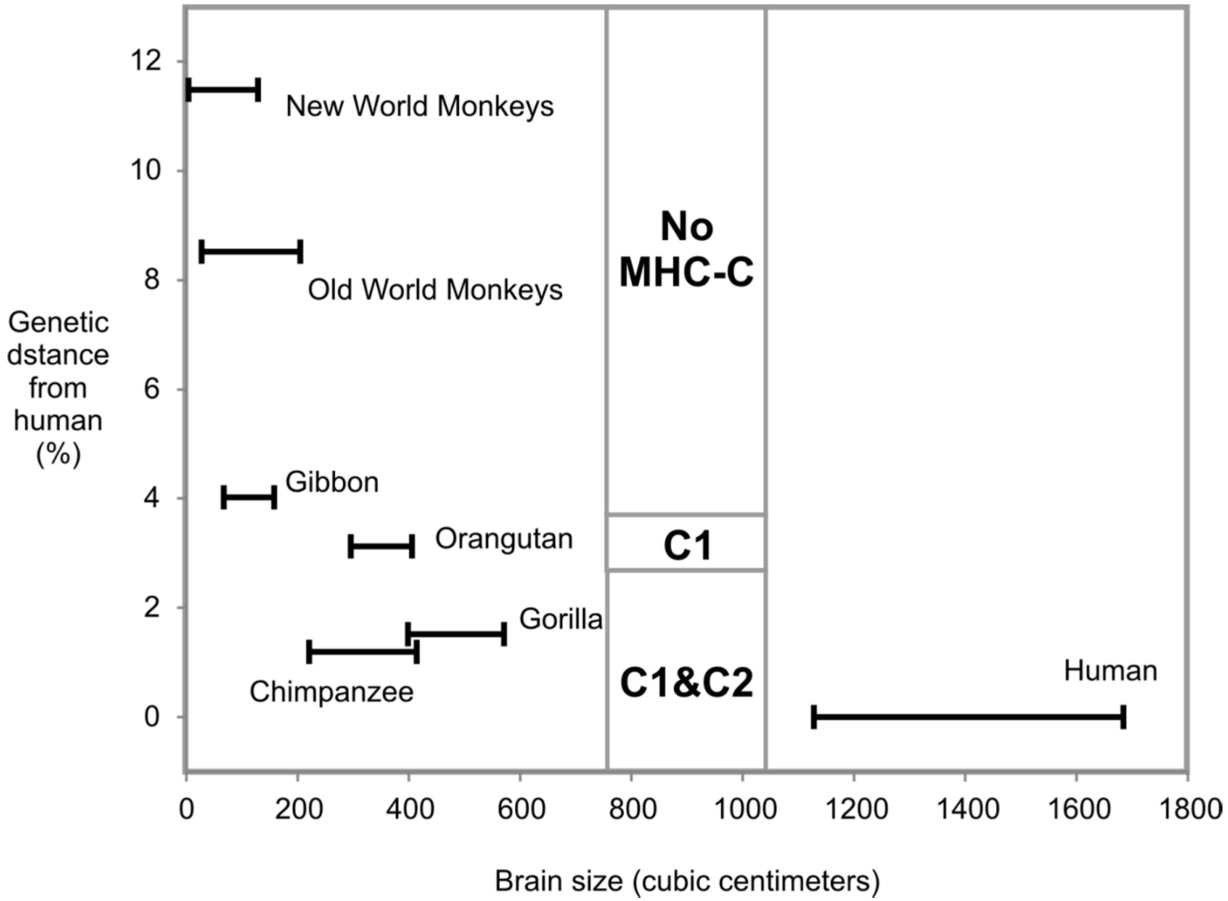
Evolution of larger brains required co-evolution of an increasingly larger supply of blood to the placenta. Increasing invasion is seen in apes and human.

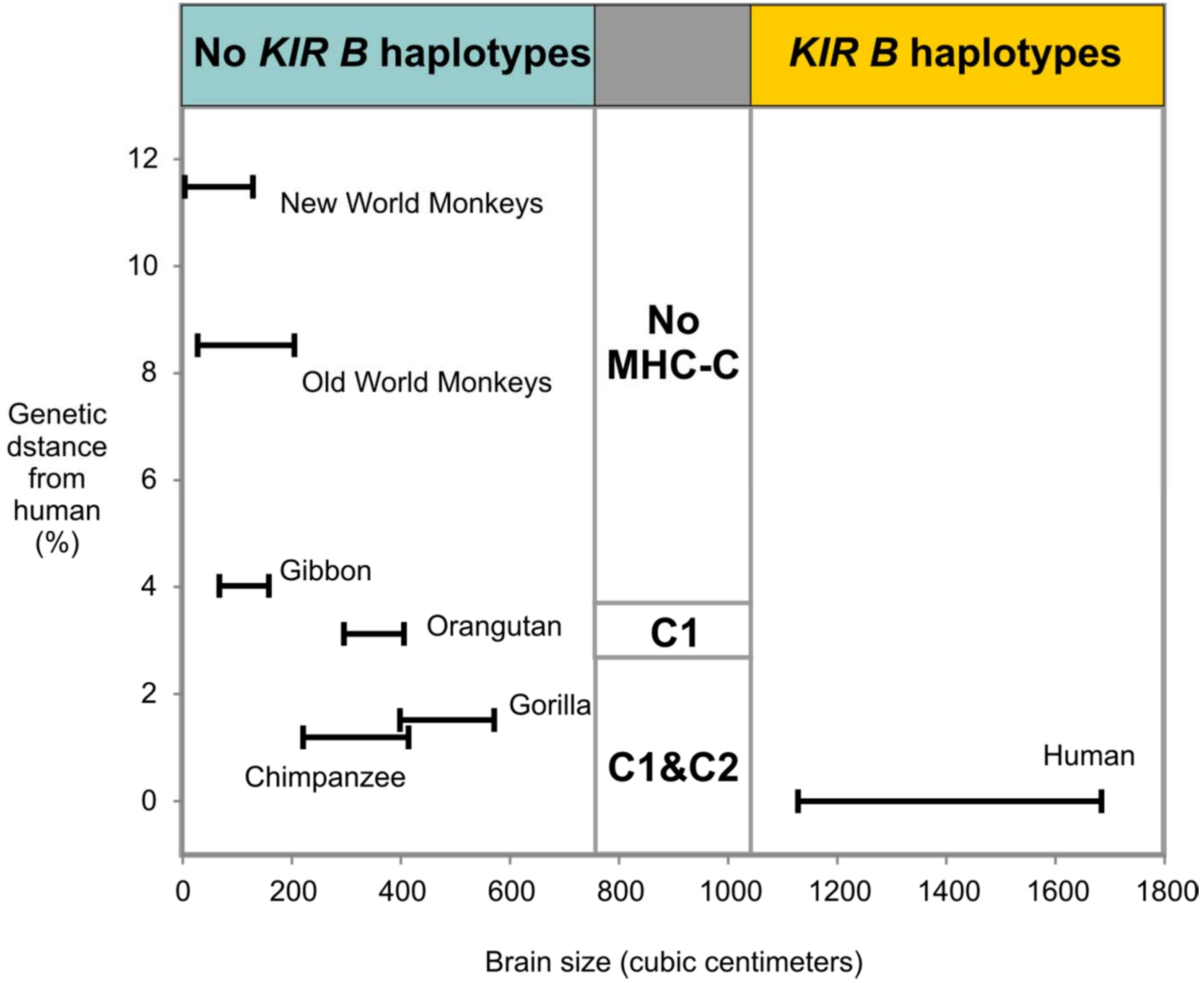



Genetic dstance from human (%)
12
10
8
6
4
2
0
New World Monkeys
Old World Monkeys
Gibbon
Orangutan
Gorilla
Chimpanzee
Human
0
200
400
600
800
1000
1200
1400
1600
1800
Brain size (cubic centimeters)

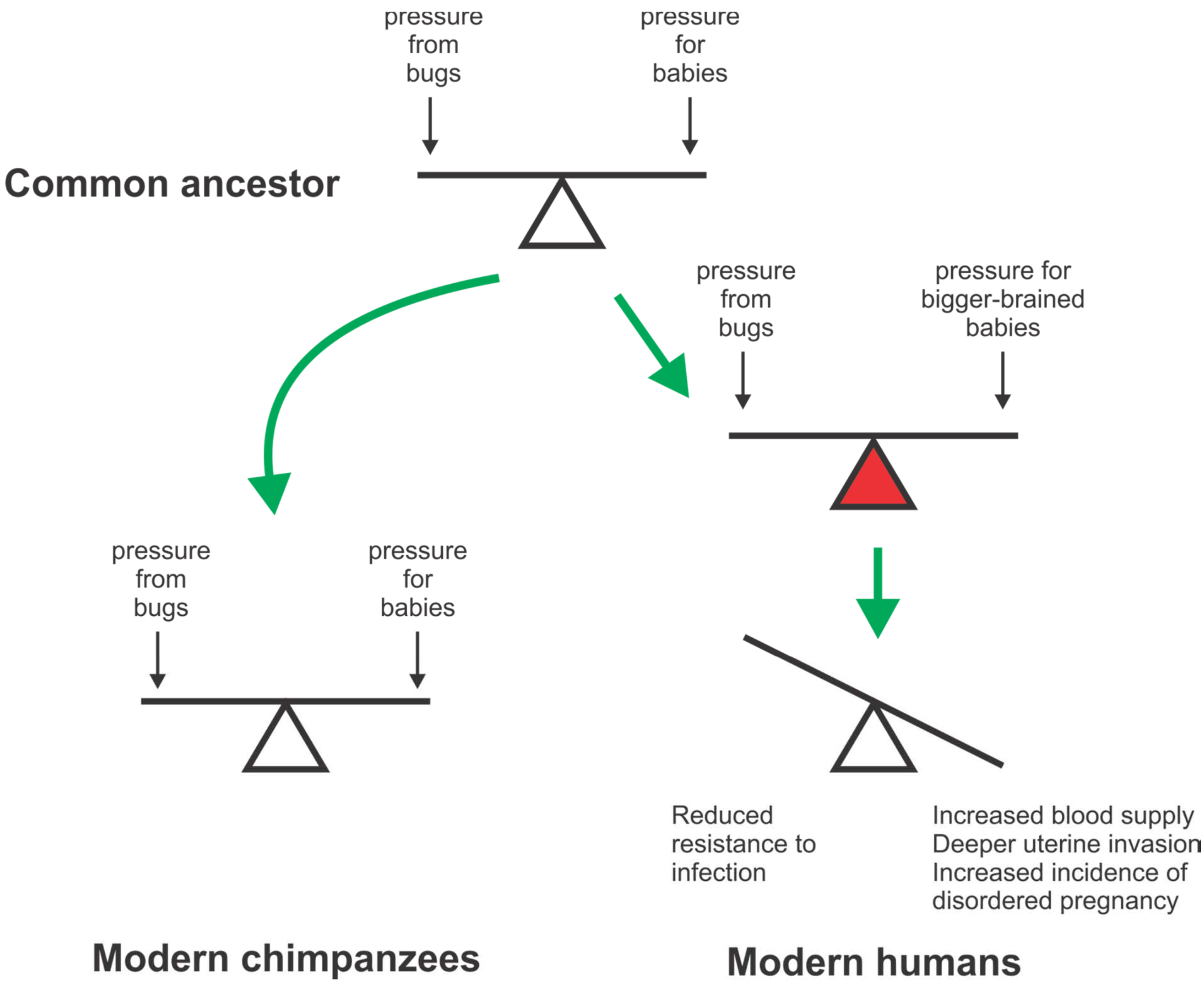

12
10
8
6
4
2
0
Genetic dstance from human (%)
New World Monkeys
Old World Monkeys
Gibbon
Orangutan
Gorilla
Chimpanzee
Human
No MHC-C
0
200
400
600
800
1000
1200
1400
1600
1800
Brain size (cubic centimeters)


Genetic dstance from human (%)
12
10
8
6
4
2
0
New World Monkeys
Old World Monkeys
Gibbon
Orangutan
Gorilla
Chimpanzee
Human
No MHC-C
C1
0
200
400
600
800
1000
1200
1400
1600
1800
Brain size (cubic centimeters)


Genetic dstance from human (%)
12
10
8
6
4
2
0
New World Monkeys
Old World Monkeys
Gibbon
Orangutan
Gorilla
Chimpanzee
No MHC-C
C1
C1&C2
Human
0
200
400
600
800
1000
1200
1400
1600
1800
Brain size (cubic centimeters)


No *KIR B* haplotypes
KIR B haplotypes
No MHC-C
C1
C1&C2
New World Monkeys
Old World Monkeys
Gibbon
Orangutan
Gorilla
Chimpanzee
Human
Genetic dstance from human (%)
12
10
8
6
4
2
0
0
200
400
600
800
1000
1200
1400
1600
1800
Brain size (cubic centimeters)

How building bigger brains could have driven the human *KIR* compromise between immunity and reproduction



Common ancestor

pressure from bugs

pressure for babies

pressure from bugs

pressure for bigger-brained babies

Modern chimpanzees

pressure from bugs

pressure for babies

Modern humans

Reduced resistance to infection

Increased blood supply
Deeper uterine invasion
Increased incidence of disordered pregnancy

Observations from Genome Comparison

Observations from Genome Comparison

[1] ~ 5% of mammalian genes are genes of the immune system.

Observations from Genome Comparison

[1] ~ 5% of mammalian genes are genes of the immune system.

[2] Comparison of the mouse and human genomes identified two classes of genes that differ both in number and nucleotide sequence: genes of the immune system and genes of the reproductive system. *Waterston 2002 Nature*

Observations from Genome Comparison

[1] ~ 5% of mammalian genes are genes of the immune system.

[2] Comparison of the mouse and human genomes identified two classes of genes that differ both in number and nucleotide sequence: genes of the immune system and genes of the reproductive system. *Waterston 2002 Nature*

[3] The combination of immune defence and reproduction is essential for the health and survival of individuals, populations and species.

Observations from Genome Comparison

[1] ~ 5% of mammalian genes are genes of the immune system.

[2] Comparison of the mouse and human genomes identified two classes of genes that differ both in number and nucleotide sequence: genes of the immune system and genes of the reproductive system. *Waterston 2002 Nature*

[3] The combination of immune defence and reproduction is essential for the health and survival of individuals, populations and species.

[4] The class I genes of the major histocompatibility complex (MHC) are the most variable and rapidly evolving genes in mammalian genomes.

Observations from Genome Comparison

[1] ~ 5% of mammalian genes are genes of the immune system.

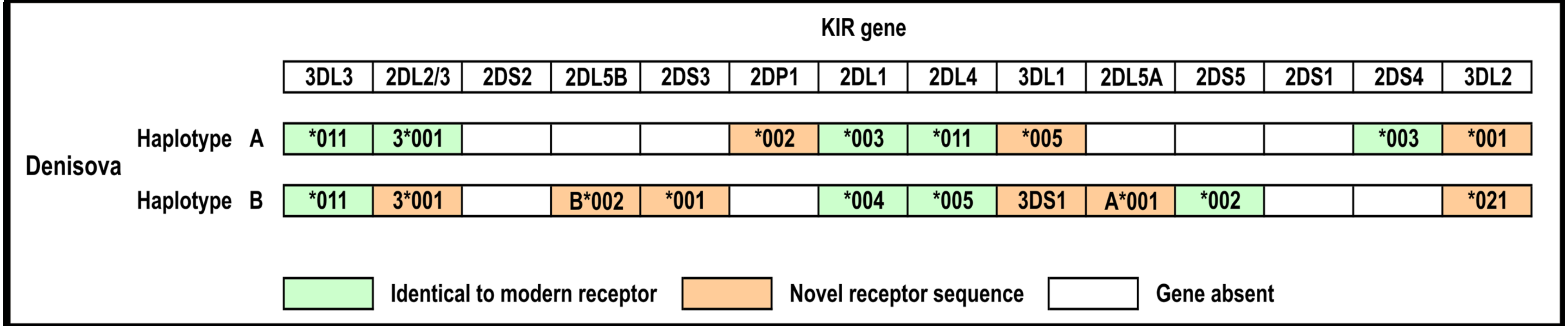
[2] Comparison of the mouse and human genomes identified two classes of genes that differ both in number and nucleotide sequence: genes of the immune system and genes of the reproductive system. *Waterston 2002 Nature*

[3] The combination of immune defence and reproduction is essential for the health and survival of individuals, populations and species.

[4] The class I genes of the major histocompatibility complex (MHC) are the most variable and rapidly evolving genes in mammalian genomes.

[5] MHC class I molecules function as ligands for the receptors of natural killer cells and killer T cells and contribute to both immune defence and reproduction.

Archaic Denisovan & Extant Immunogeneticist Have similar *A* and *B KIR* haplotypes

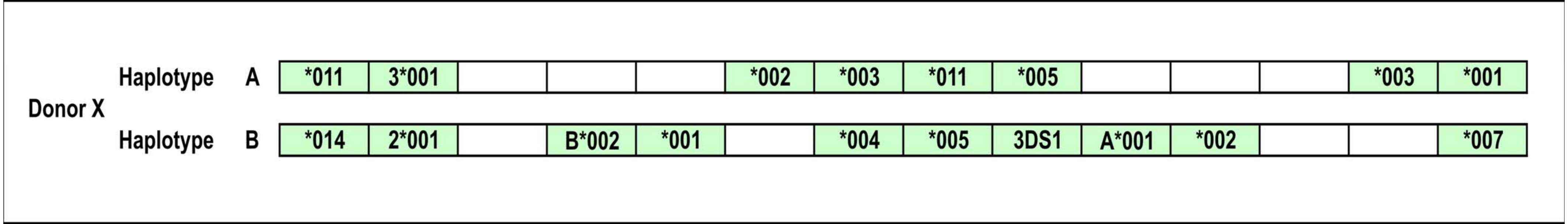


KIR gene

		3DL3	2DL2/3	2DS2	2DL5B	2DS3	2DP1	2DL1	2DL4	3DL1	2DL5A	2DS5	2DS1	2DS4	3DL2
Denisova	Haplotype A	🟩 *011	🟩 3*001	□	□	□	🟧 *002	🟩 *003	🟩 *011	🟧 *005	□	□	□	🟩 *003	🟧 *001
	Haplotype B	🟩 *011	🟧 3*001	□	🟧 B*002	🟧 *001	□	🟩 *004	🟩 *005	🟧 3DS1	🟧 A*001	🟩 *002	□	□	🟧 *021

🟩 Identical to modern receptor 🟧 Novel receptor sequence □ Gene absent

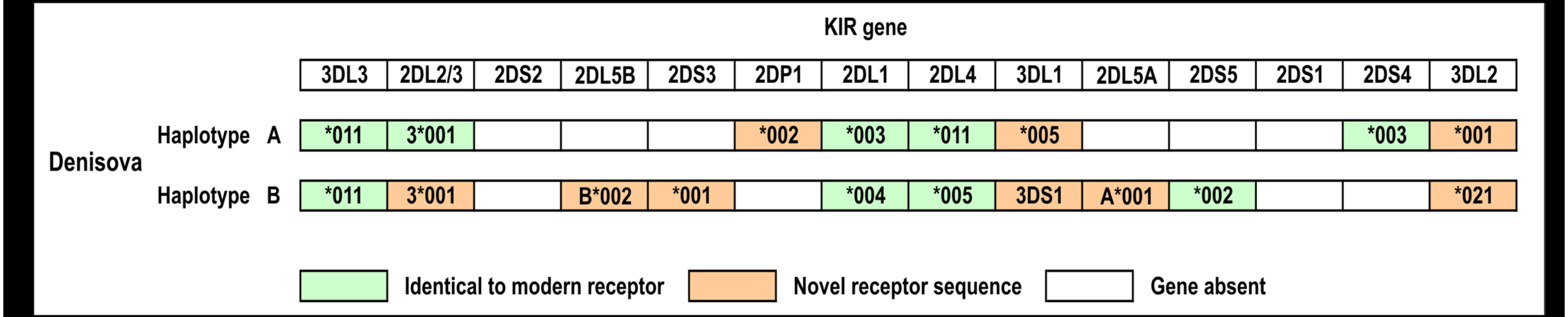
Full allele-level KIR genotype of Denisova



		3DL3	2DL2/3	2DS2	2DL5B	2DS3	2DP1	2DL1	2DL4	3DL1	2DL5A	2DS5	2DS1	2DS4	3DL2
Donor X	Haplotype A	🟩 *011	🟩 3*001	□	□	□	🟩 *002	🟩 *003	🟩 *011	🟩 *005	□	□	□	🟩 *003	🟩 *001
	Haplotype B	🟩 *014	🟩 2*001	□	🟩 B*002	🟩 *001	□	🟩 *004	🟩 *005	🟩 3DS1	🟩 A*001	🟩 *002	□	□	🟩 *007

Full allele-level KIR genotype of a Modern Human

Denisova has *KIR A* and *B* haplotypes



KIR gene

		3DL3	2DL2/3	2DS2	2DL5B	2DS3	2DP1	2DL1	2DL4	3DL1	2DL5A	2DS5	2DS1	2DS4	3DL2
Denisova	Haplotype A	🟩 *011	🟩 3*001	⬜	⬜	⬜	🟧 *002	🟩 *003	🟩 *011	🟧 *005	⬜	⬜	⬜	🟩 *003	🟧 *001
	Haplotype B	🟩 *011	🟧 3*001	⬜	🟧 B*002	🟧 *001	⬜	🟩 *004	🟩 *005	🟩 3DS1	🟧 A*001	🟩 *002	⬜	⬜	🟧 *021

🟩 Identical to modern receptor 🟧 Novel receptor sequence ⬜ Gene absent

Full allele-level KIR genotype of Denisova