Boosting Eurasian Immunity by Alliance and Dalliance of Humans, Ancient and Modern

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Evolutionary Origins of Compartmentalized Cells

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Paul Norman

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Hugo Hilton

Richard Green, University of California, Santa Cruz

Ashley Moffett, University of Cambridge

Bone-marrow transplant donor registries worldwide

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[1] HLA class I : variable ligands for lymphocyte receptors.

[2] Human migration Out-of-Siberia to colonize the Americas

[3] Human migration Out-of-Africa to colonize Eurasia.

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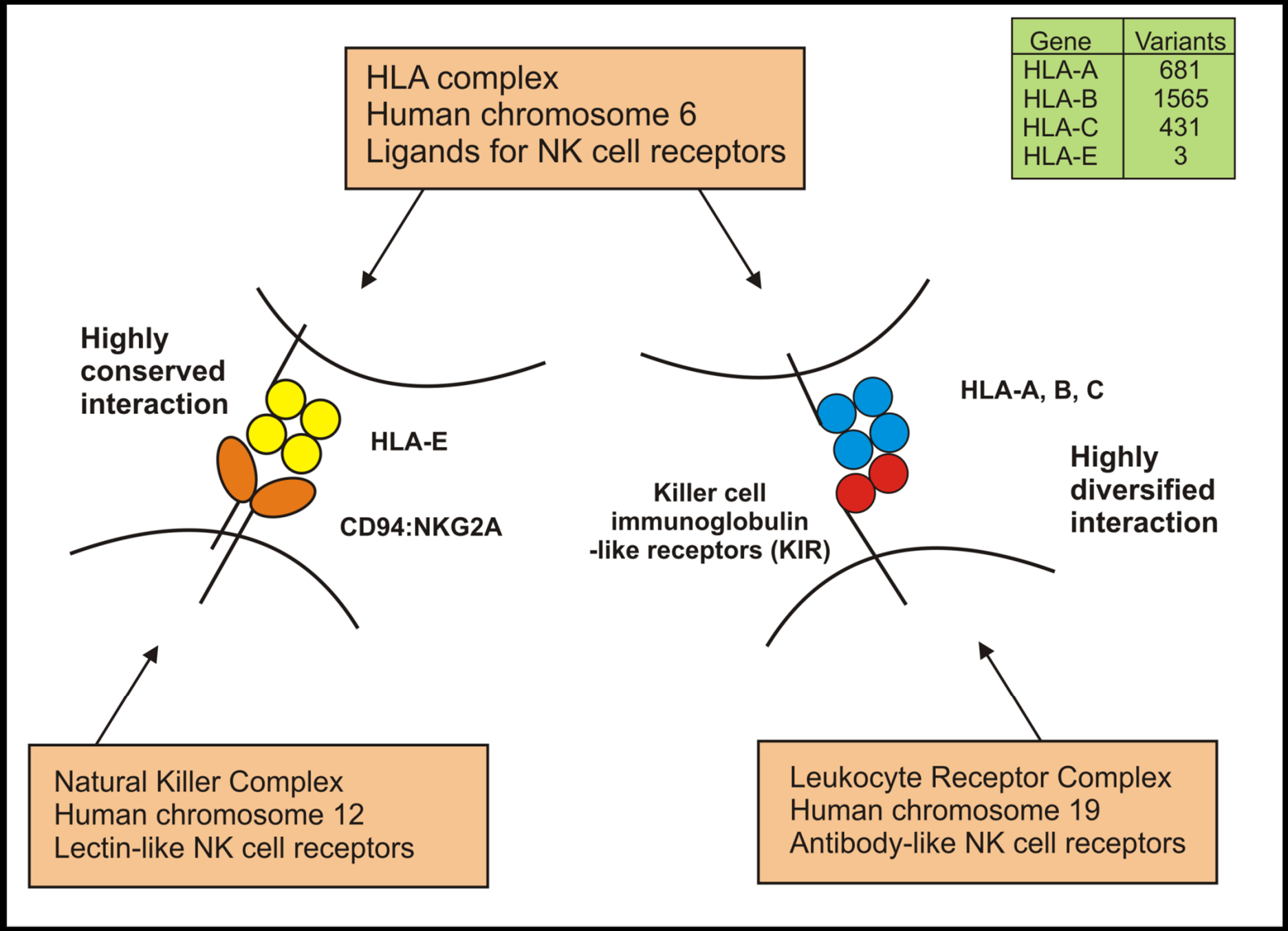
[5] MHC class I molecules function as ligands for the receptors of natural killer cells and killer T cells and contribute to both immune defence and reproduction.

Three Genomic Complexes Encode the Ligands and Receptors that Control and Diversify Human NK-cell Function



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

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HLA class I variability concentrates in the binding site for peptides

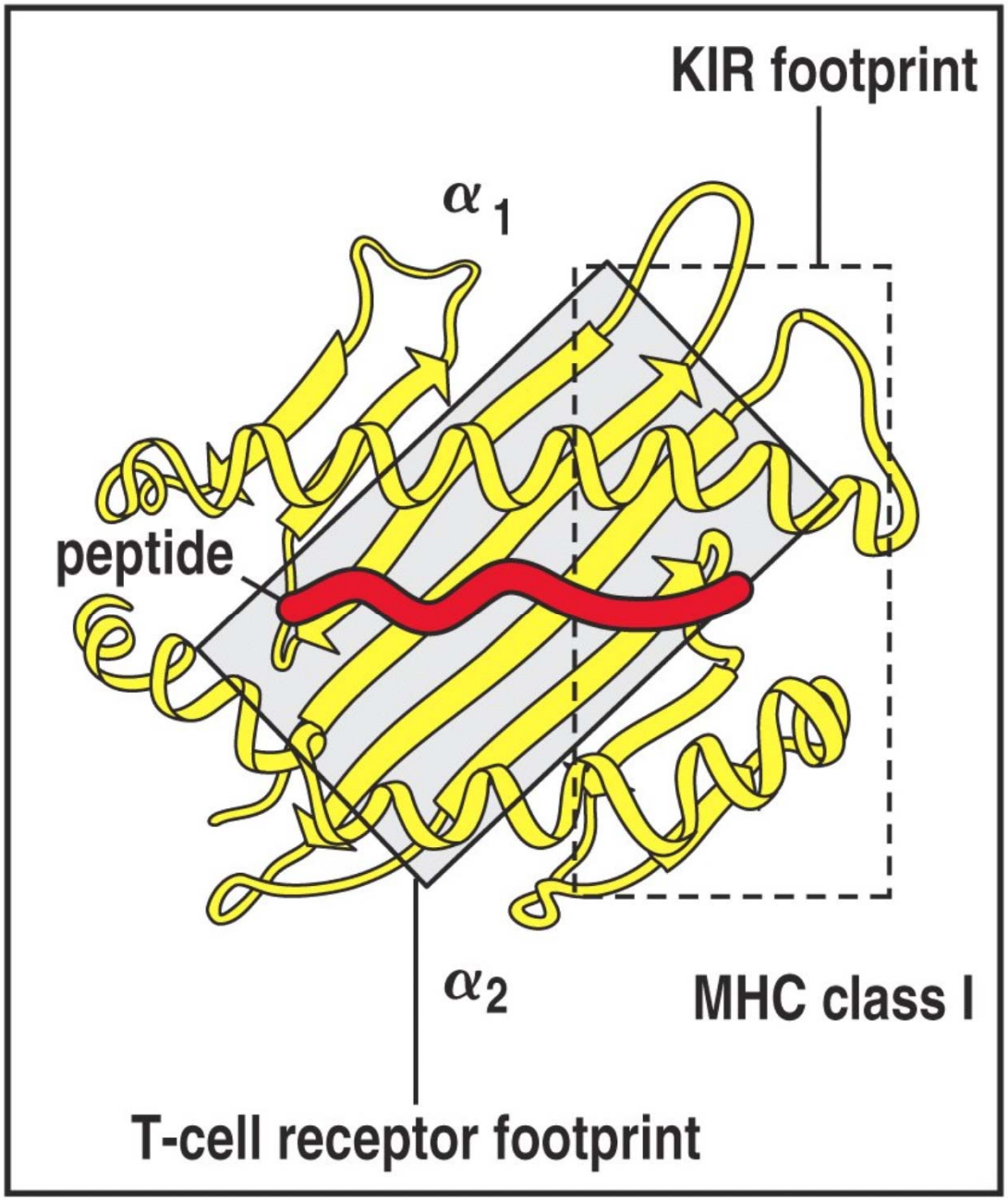

Figure 8-30 The Immune System, 2/e (© Garland Science 2005)

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[9] Most individuals have different HLA types and thus distinctive immune systems with different strengths and weaknesses.

How much HLA class I diversity does a human population need to survive?

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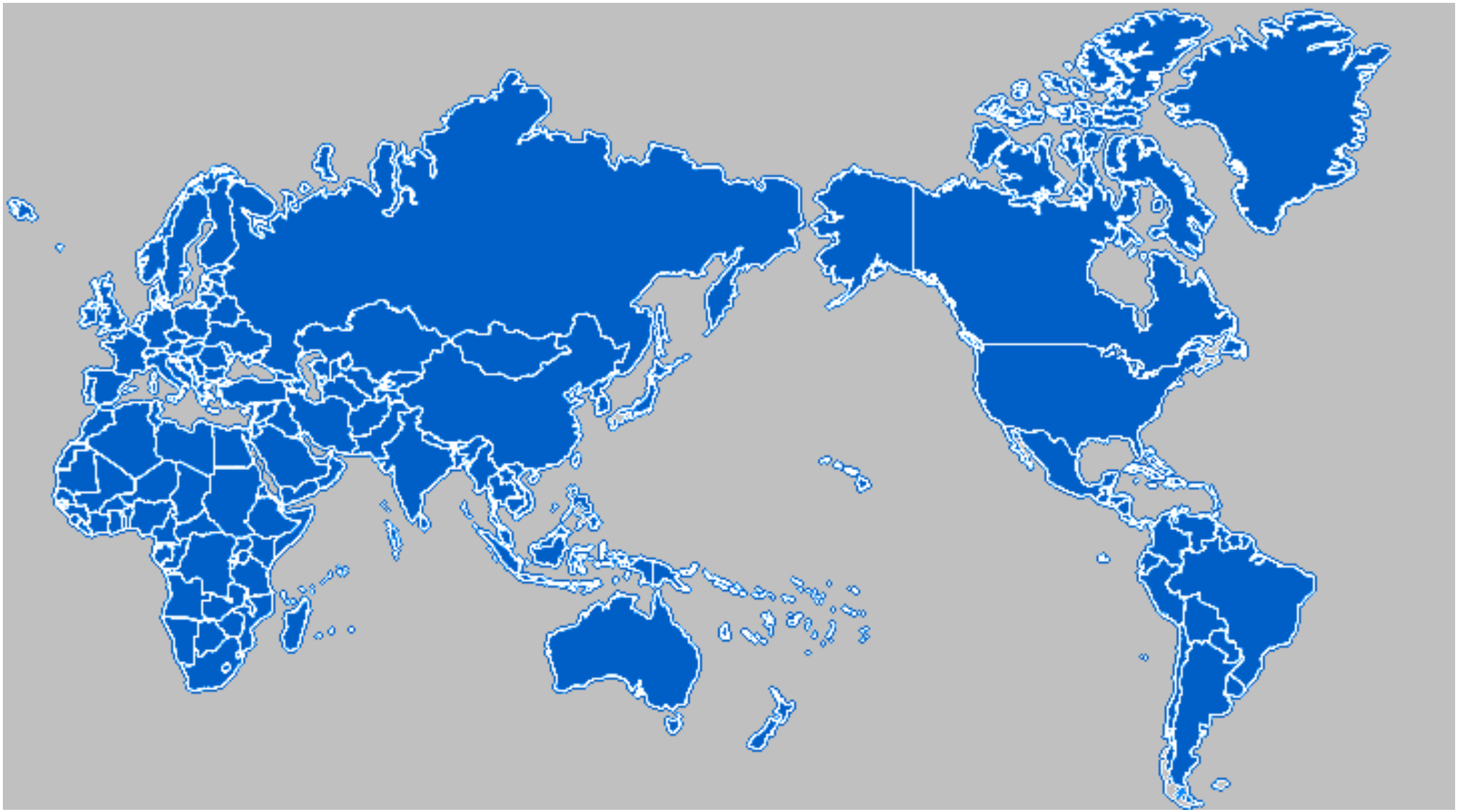

~17,000 years ago Asian migrants from Siberia were the first human populations to survive long term in America

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[5] A second colonization of the Americas began in 1492 with the arrival by boat of Europeans, precipitating >500 years of conflict, disease, and bottleneck for Amerindian populations.

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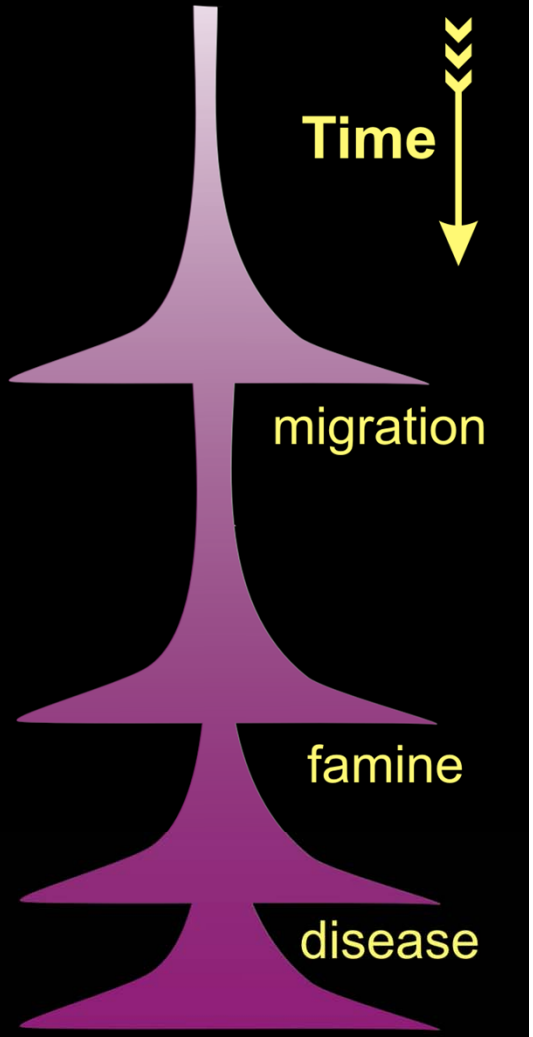
The Yucpa population of Venezuela have a typical Amerindian history

Yucpa

Venezuela



HLA class I in Yucpa Amerindians

HLA-A			*HLA-B*			*HLA-C*		
Allele	KIR Ligand	Frequency %	Allele	KIR Ligand	Frequency %	Allele	KIR Ligand	Frequency %
**6801*		46.7	**3909*		41.8	**0702*	C1	76.2
**0204*		27.8	**3905*		34.4	**1503*	C2	9.8
**0212*		0.8	**5201*	Bw4	9.8	**0401*	C2	7.4
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**2402*	Bw4	17.2	**3543*		1.6	**0304*	C1	0.8
**3101*		6.5	**4002*		4.1	**0102*	C1	1.6
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Total	Bw4	17.2	Total	Bw4	9.8	Total	C1	82.8 (97)
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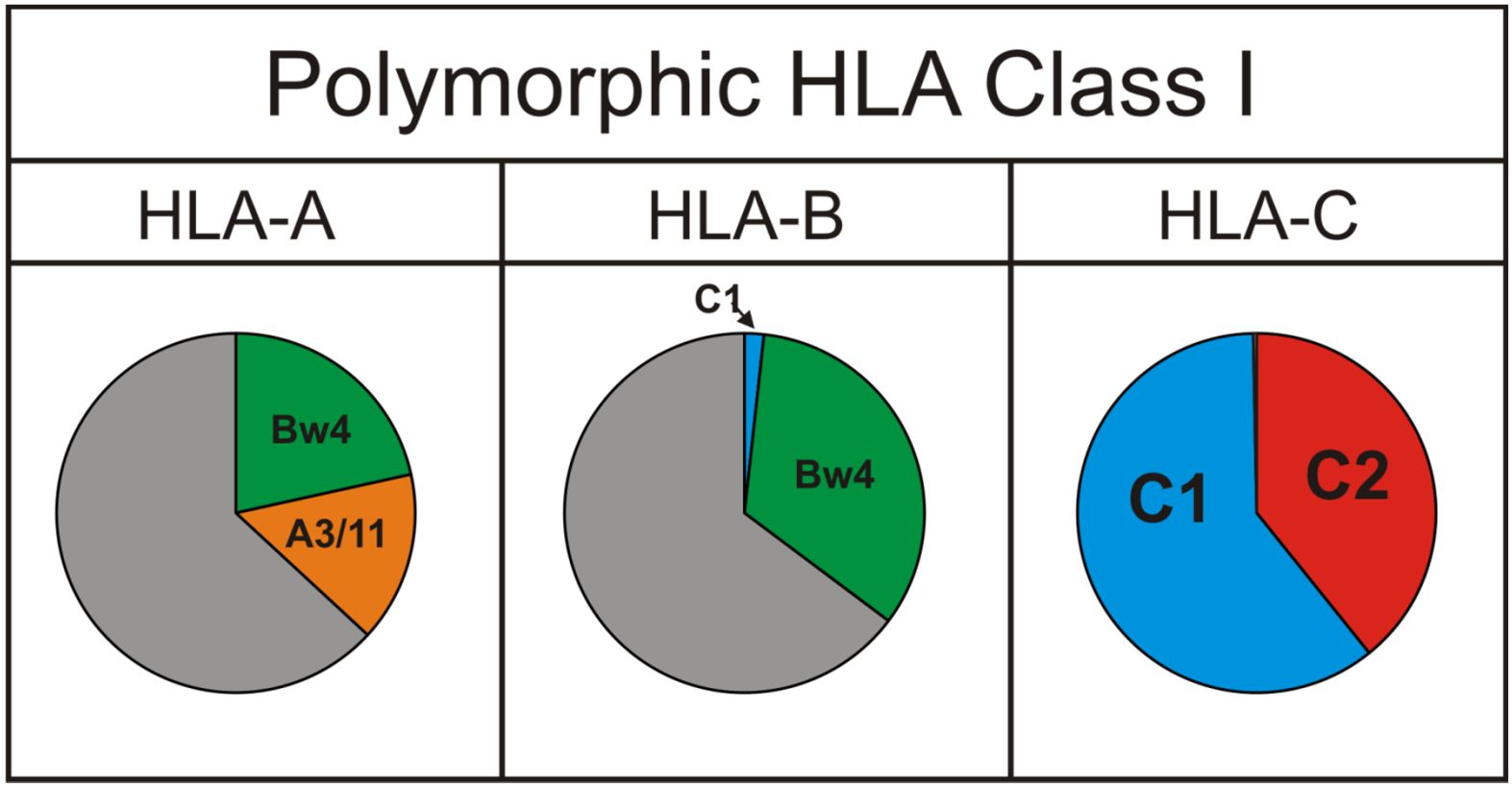
Variable NK cell receptors Recognize Four Epitopes of HLA-A,-B,and -C



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[4] Human populations fpr which HLA class I diversity falls below that observed in Amerindians either died out or were assimilated by another population.

Are there genetic benefits from the second human colonization of the Americas ?

[1] Overall the European conquest of the Americas did not greatly decrease the overall genetic diversity of Amerindians as a whole.

[2] During the early and formative period of colonisation the European populations were small and likely carried only a fraction of the genetic diversity from their population of origin.

[3] During this formative period the well-documented parenting between Europeans and Amerindians could have been mutually beneficial due to the introduction into both populations of new HLA class I variants.

[4] The degree of assimilation has varied greatly between countries and is still an ongoing evolution. For example, in many urban Mexican populations there is now an approximately 50:50 ratio of European and Amerindian HLA variants.

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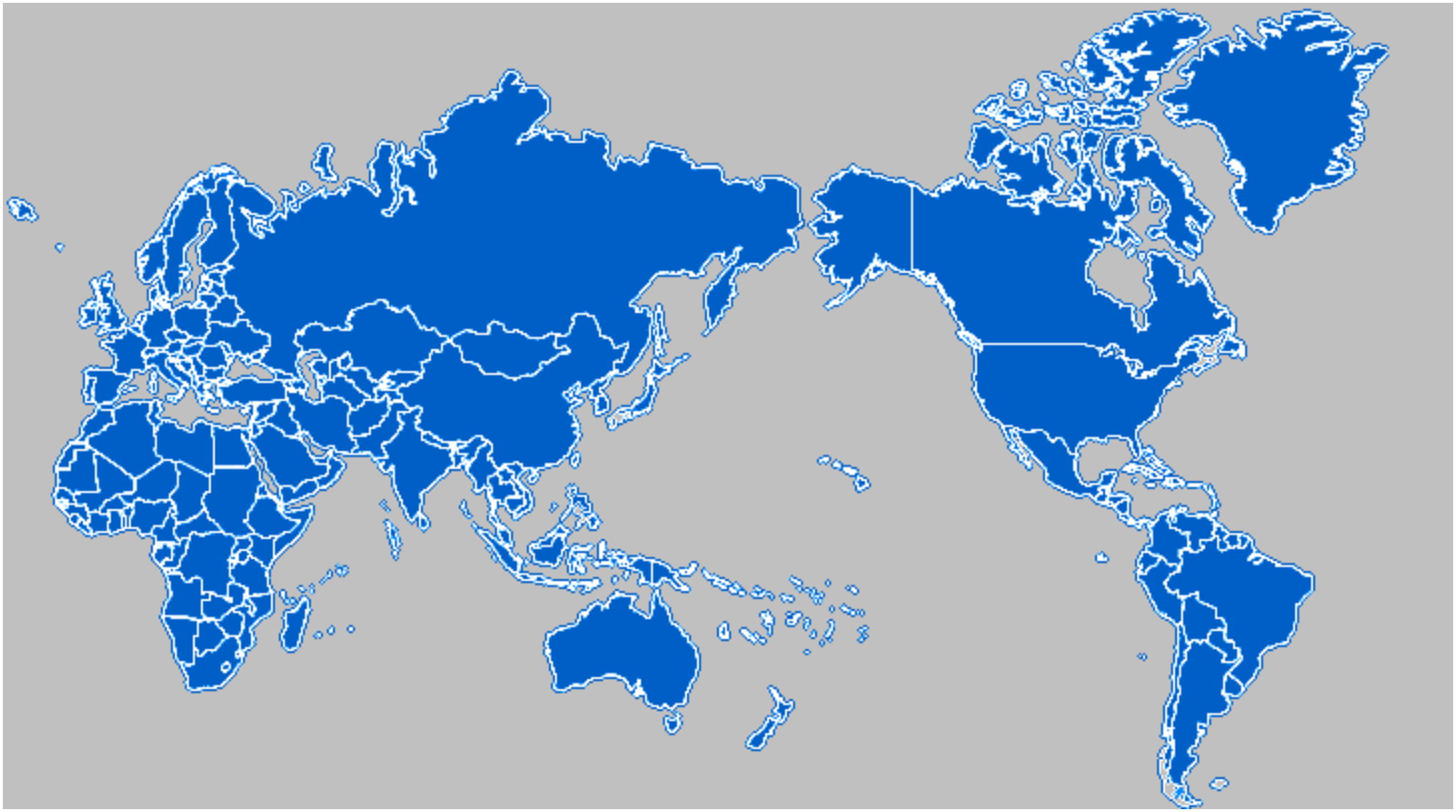
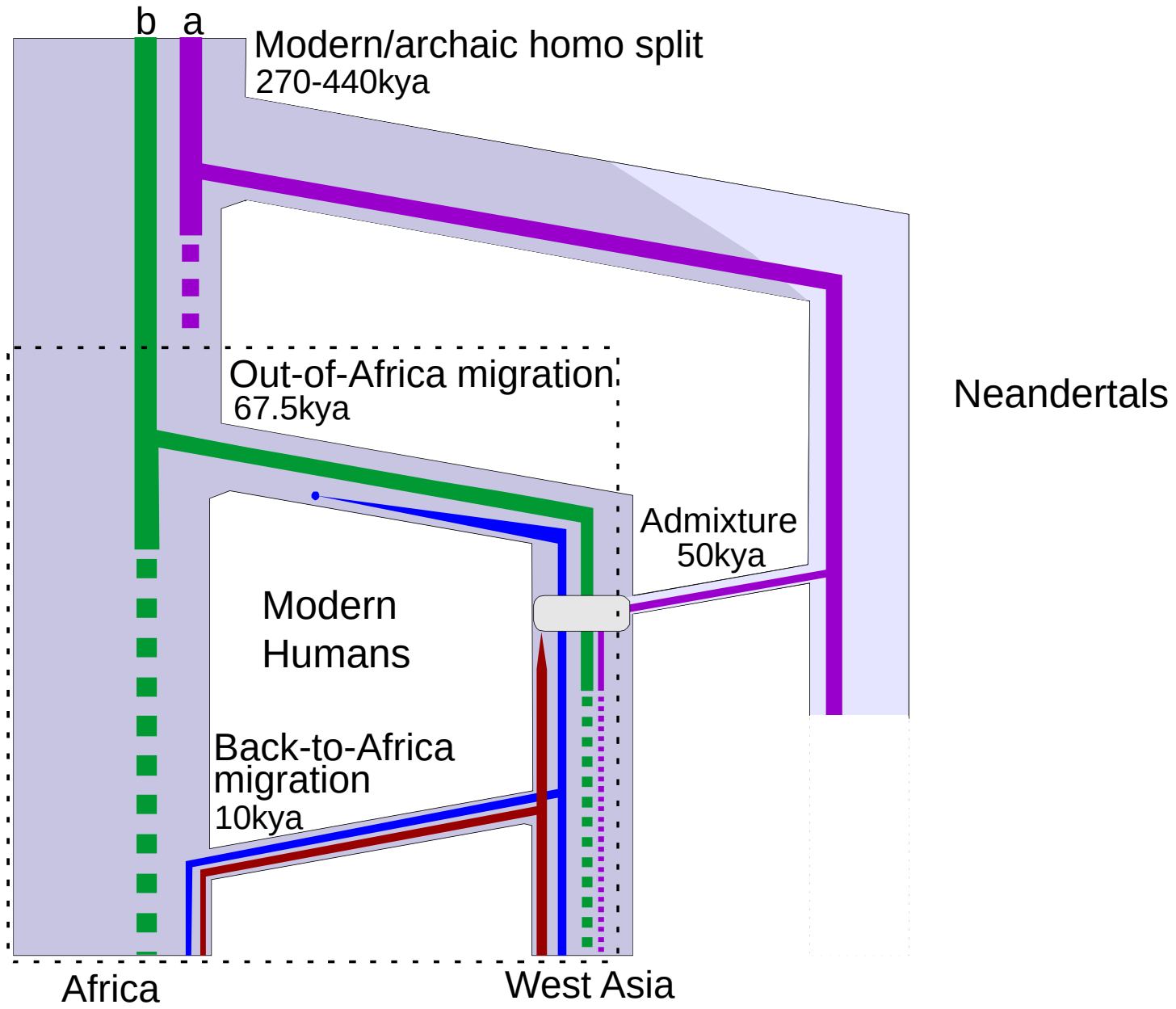
[3] Human migration Out-of-Africa to colonize Eurasia.

~350,000 years ago Neandertal ancestors went Out-of-Africa

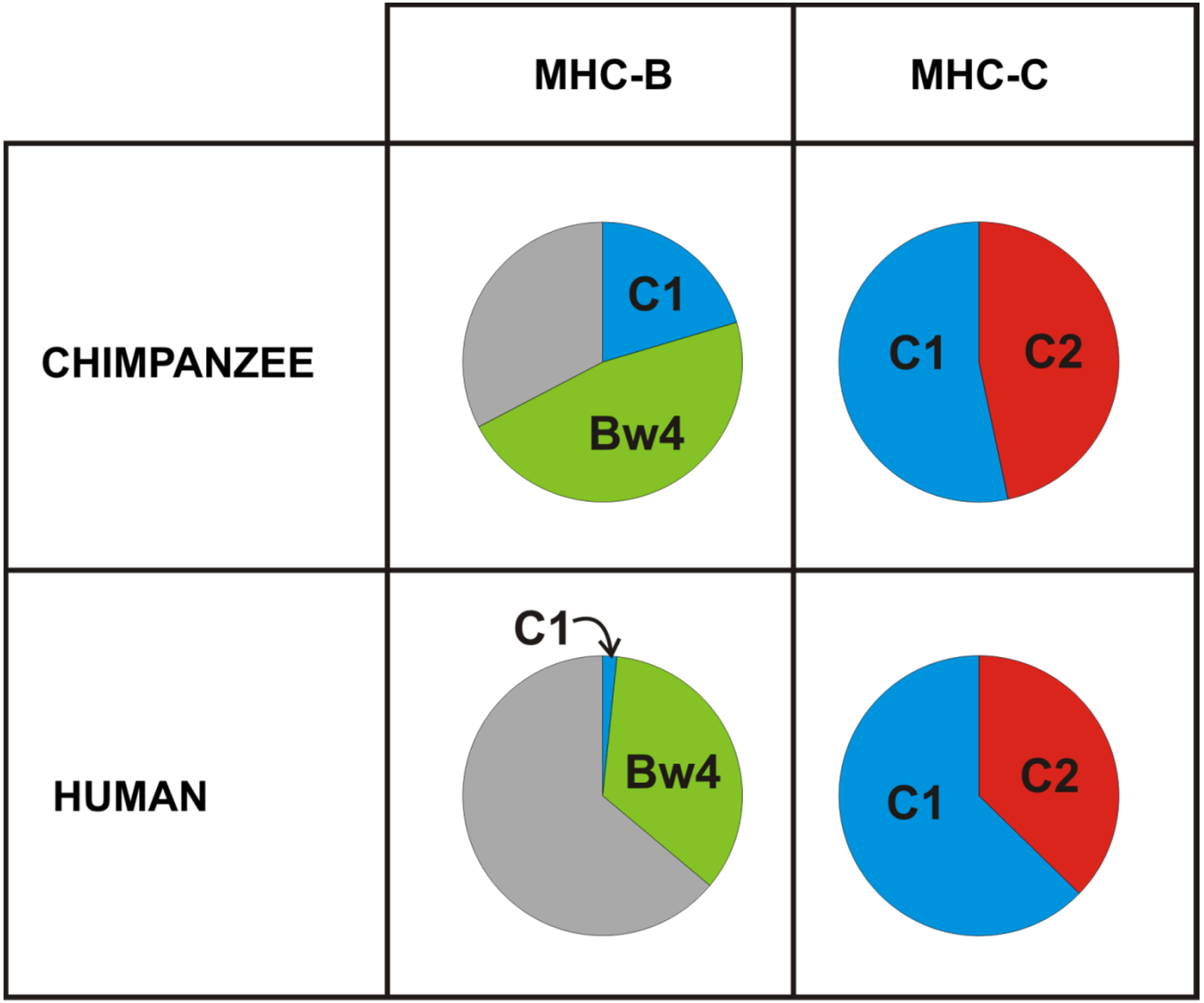


~70,000 years ago modern humans went Out-of-Africa and co-existed with Neandertals in Europe and Asia for ~30,000 years before Neandertals disappeared from the fossil record

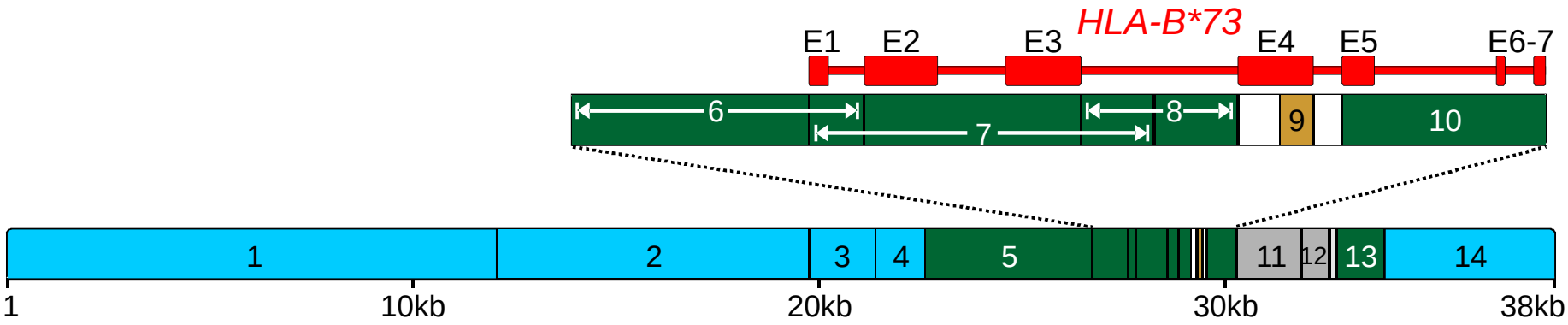
Two human migrations Out-of-Africa to colonise Europe and Asia: did modern humans Neandertals meet, mate and conflict?



HLA-B*73 is an unusual HLA-B that has the C1 Epitope, a common feature of chimpanzee HLA-B

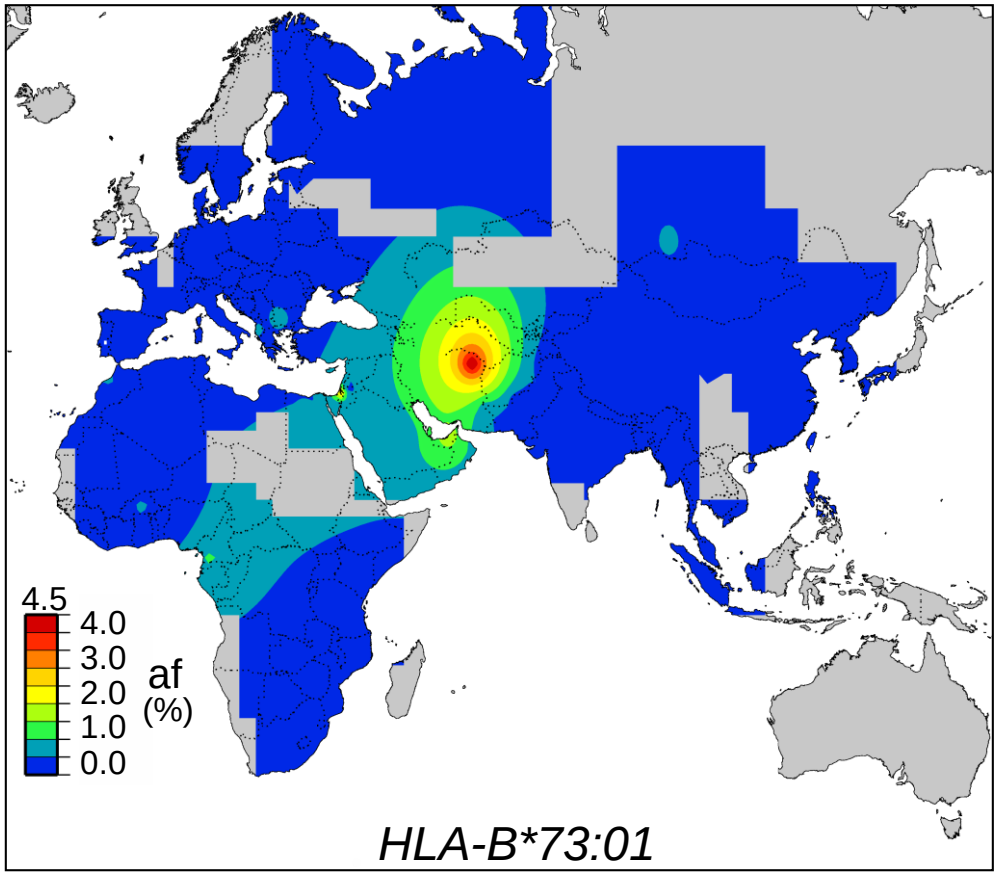


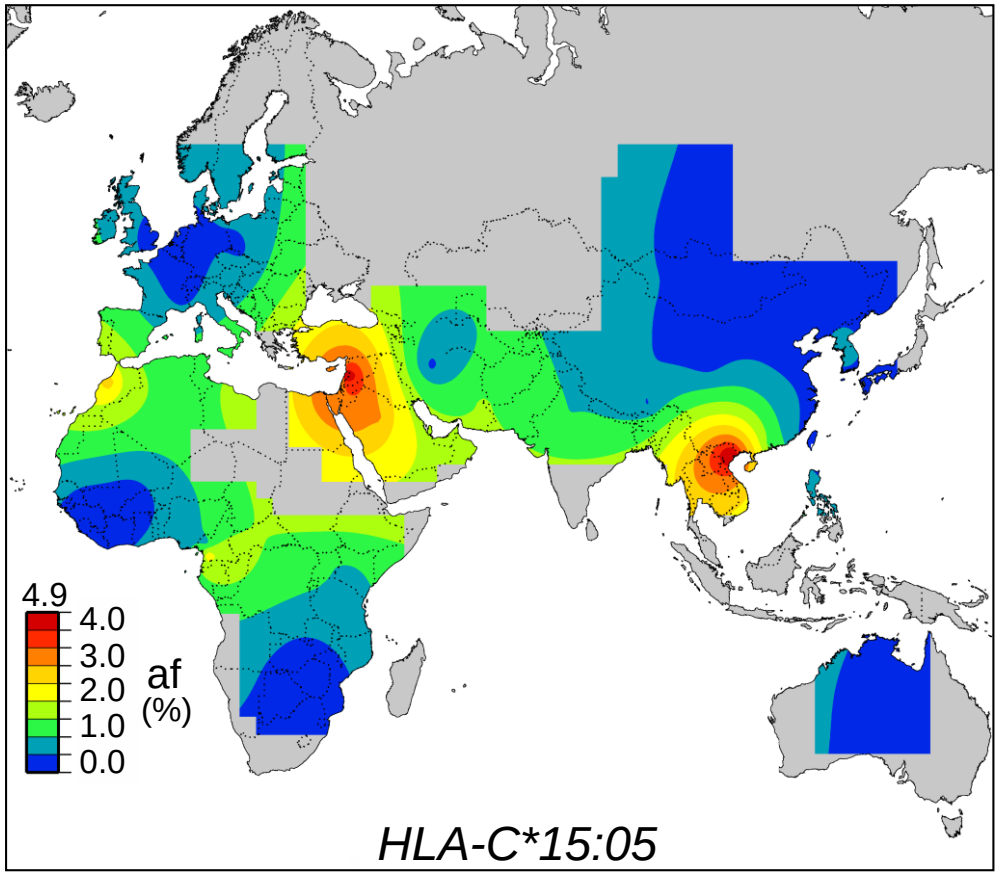
*HLA-B*73* unusually combines ancient sequence divergence with modern sequence homogeneity



Abi-Rached et al 2011 Science

*HLA-B*73* localizes to western Asia and is in strong linkage disequilibrium with *HLA-C*1505*





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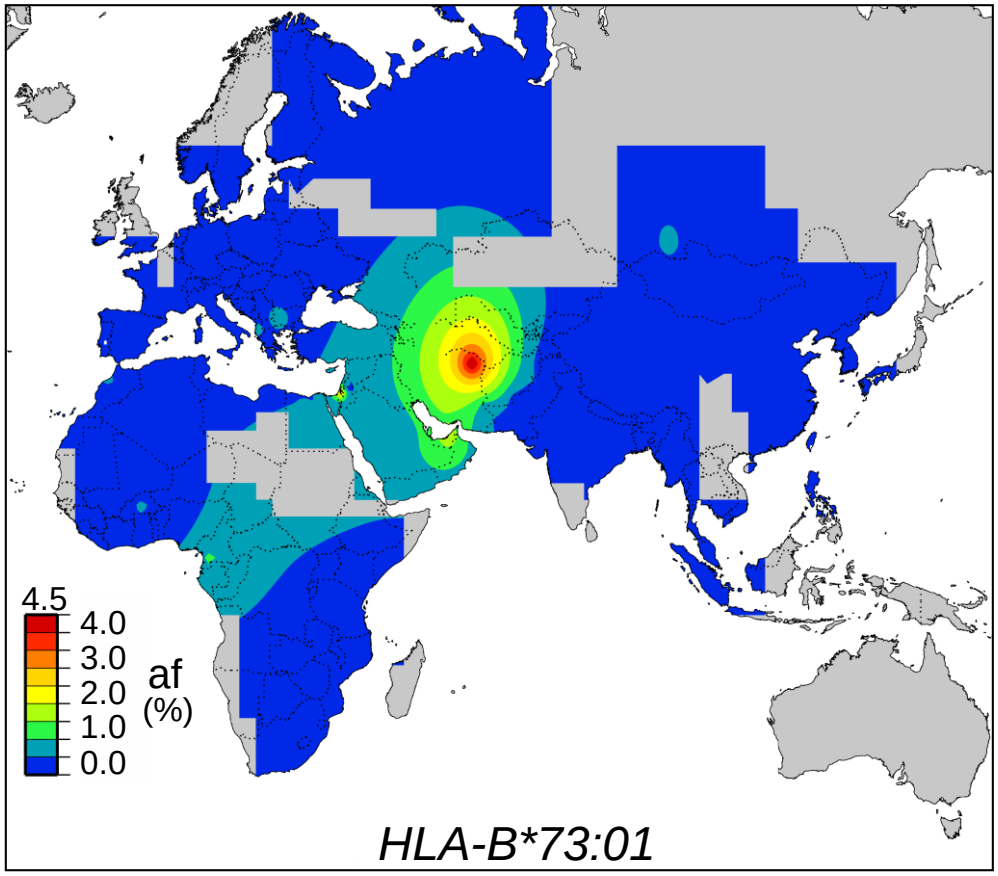
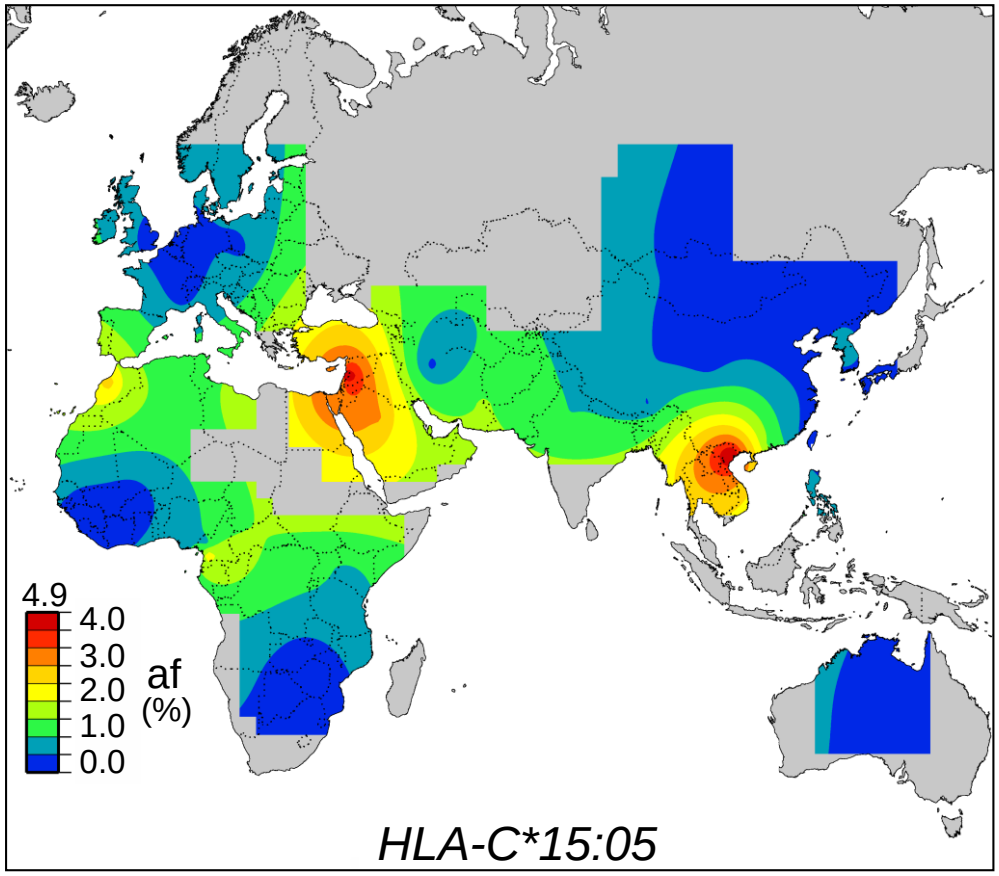
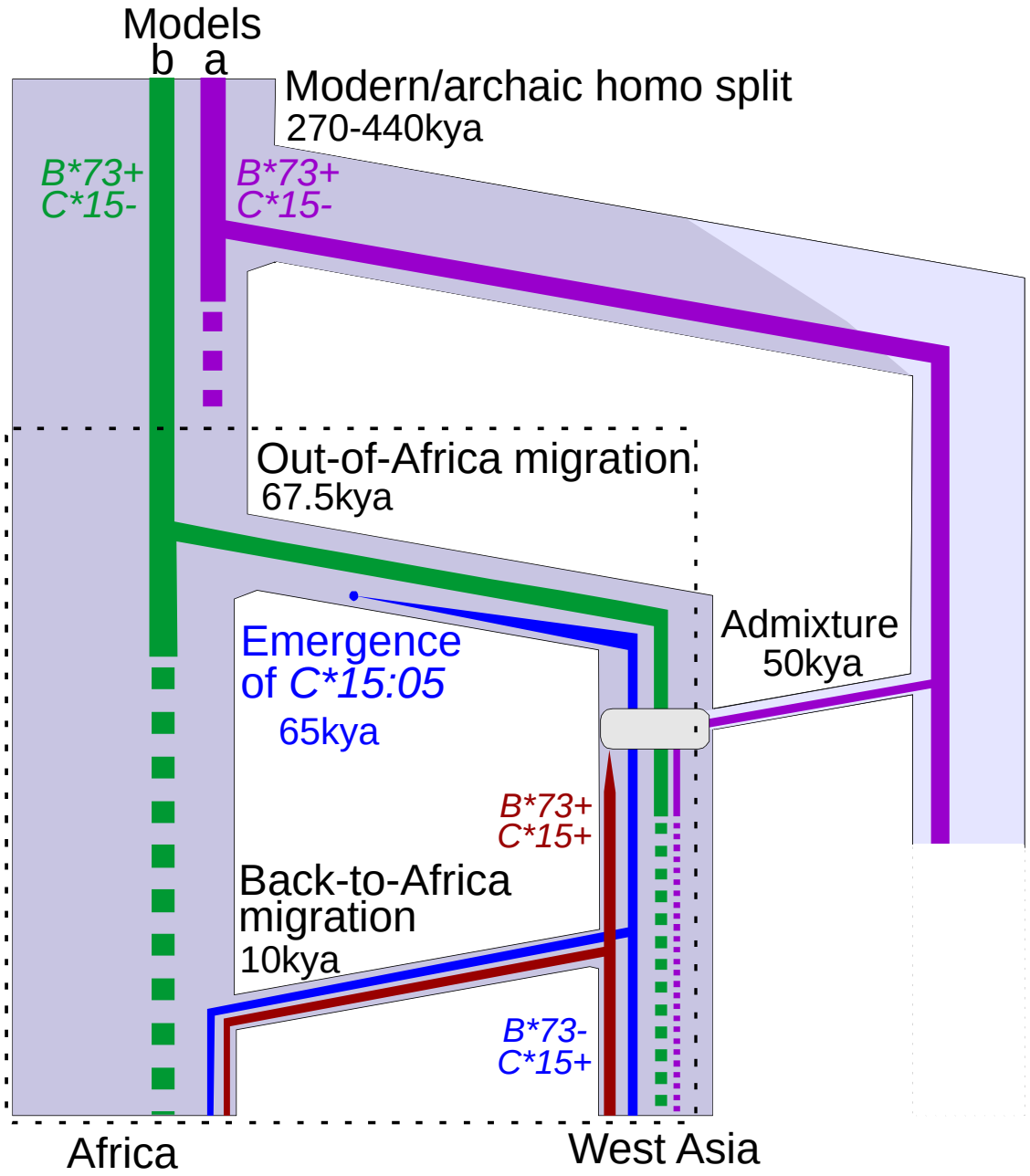




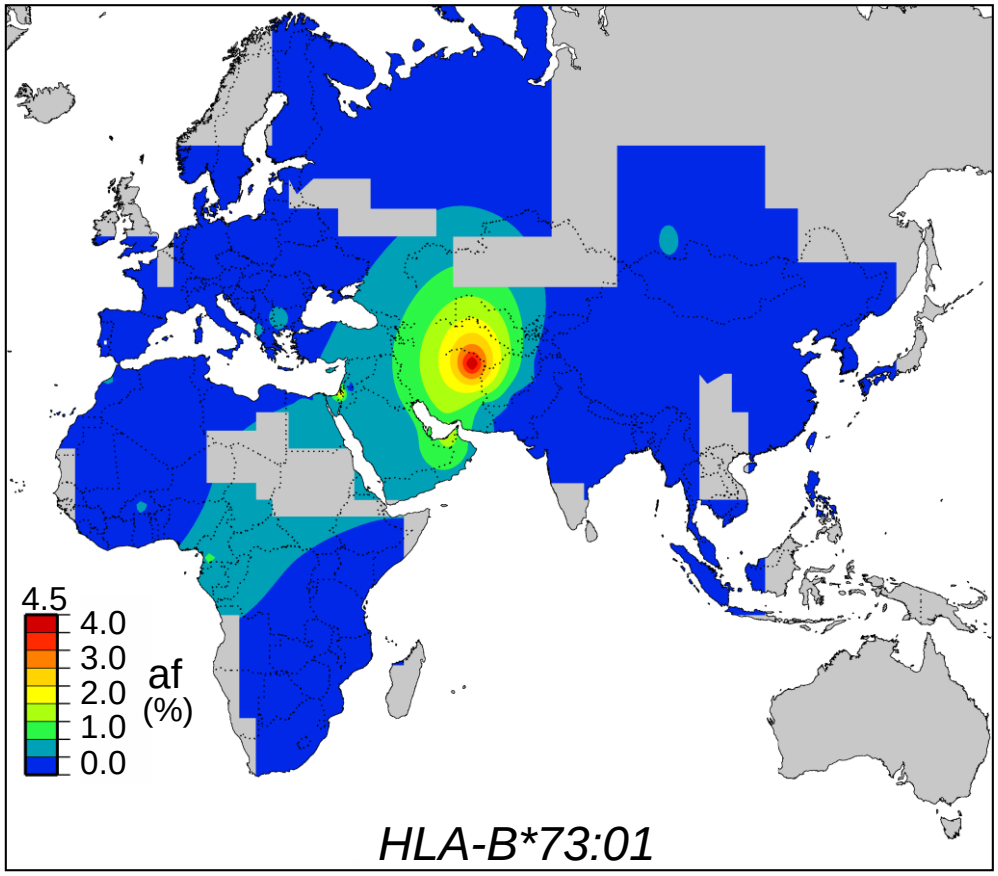
*HLA-B*73* is particularly frequent in Parsees

Its unusual properties and the results from demographic simulations point to HLA-B*73 having been passed from archaic humans to modern humans by horizontal transfer

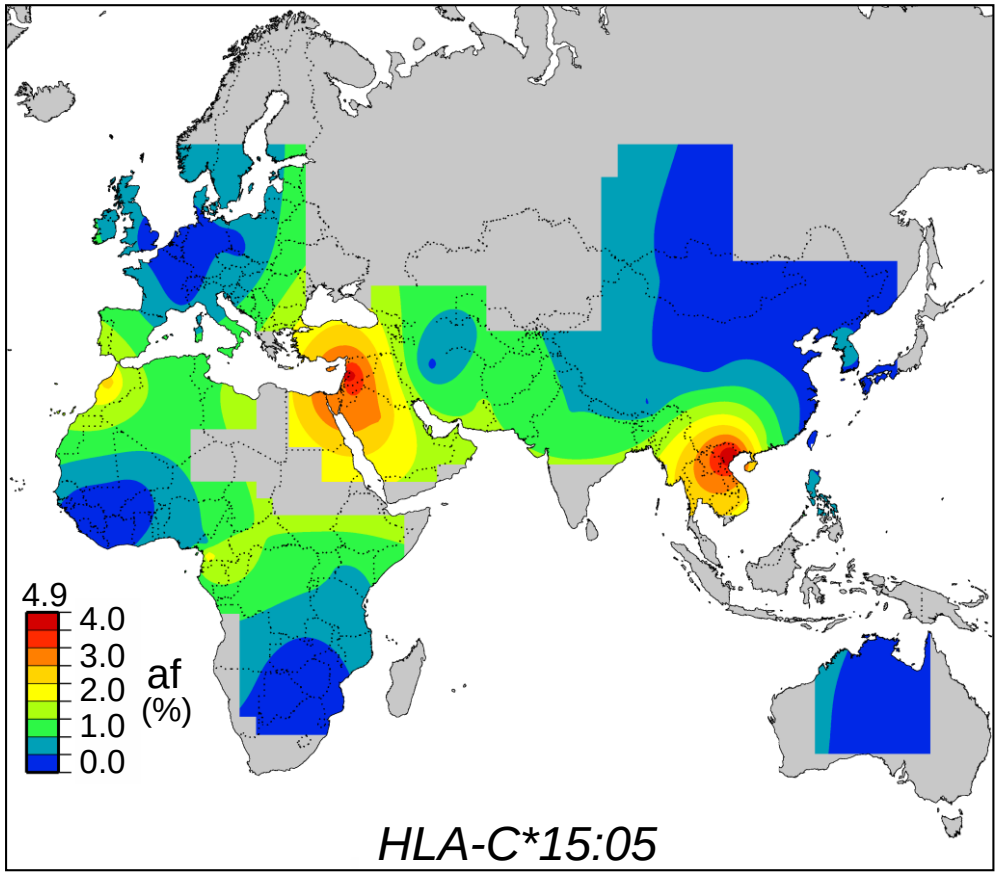


Abi-Rached et al 2011
Science 334: 89-94.

A unique functional feature of the HLA-B*7301 haplotype is that carries both the C1 and C2 epitopes



C1 epitope

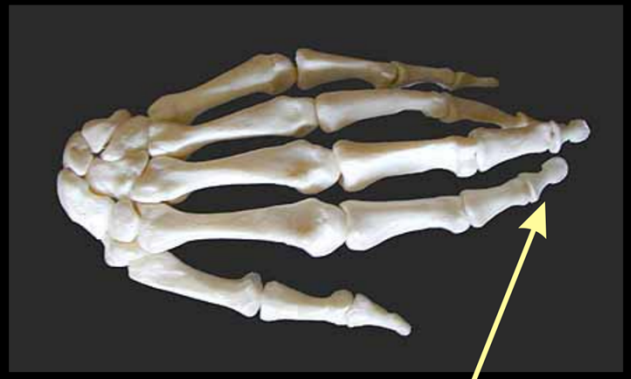


C2 epitope

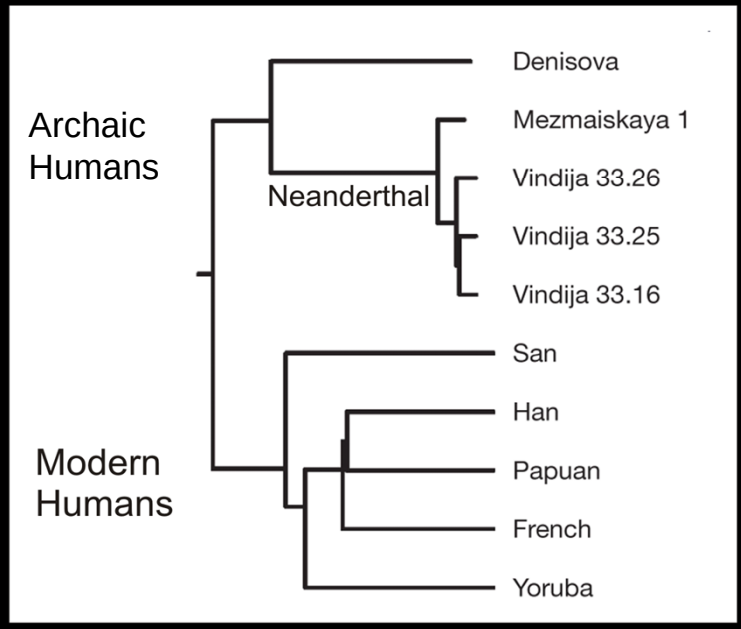
Whole Genome Sequence Comparison of Neutral Markers Gave Evidence For up to 6% Archaic DNA in Modern Eurasian Genomes

Green et al Reich et al 2010

Denisova, Neanderthal and Modern Humans all co-existed



Ancient DNA from preserved finger bone



Estimated ~4-6% Denisovan contribution to modern Melanesian genomes and 1-4% Neandertal contribution to modern Eurasian genomes.

HLA typing of the Denisovan woman.

Denisovan *HLA class I*							
Allele				Closest modern type		Next best type	
Locus	#	Coverage	Reads (#)	Name	Differences	Name	Differences
HLA-A	1	15%	15	A*02:01/03/07/48	0	A*68	7
	2	21%	17	A*11:01/53	0	A*03/*30	4
HLA-B	1	34%	35	B*15:58	3	B*46	5
	2	39%	43	B*35:63[¶]	0	B*53	9
HLA-C	1	33%	30	C*12:02:02	0	C*06	7
	2	19%	16	C*15:02/05/17 [§]	1	C*02	5

She shares five of six *HLA-A, -B, -C* alleles with modern humans

Denisovan *HLA class I*							
Allele				Closest modern type		Next best type	
Locus	#	Coverage	Reads (#)	Name	Differences	Name	Differences
HLA-A	1	15%	15	A*02:01/03/07/48	0	A*68	7
	2	21%	17	A*11:01/53	0	A*03/*30	4
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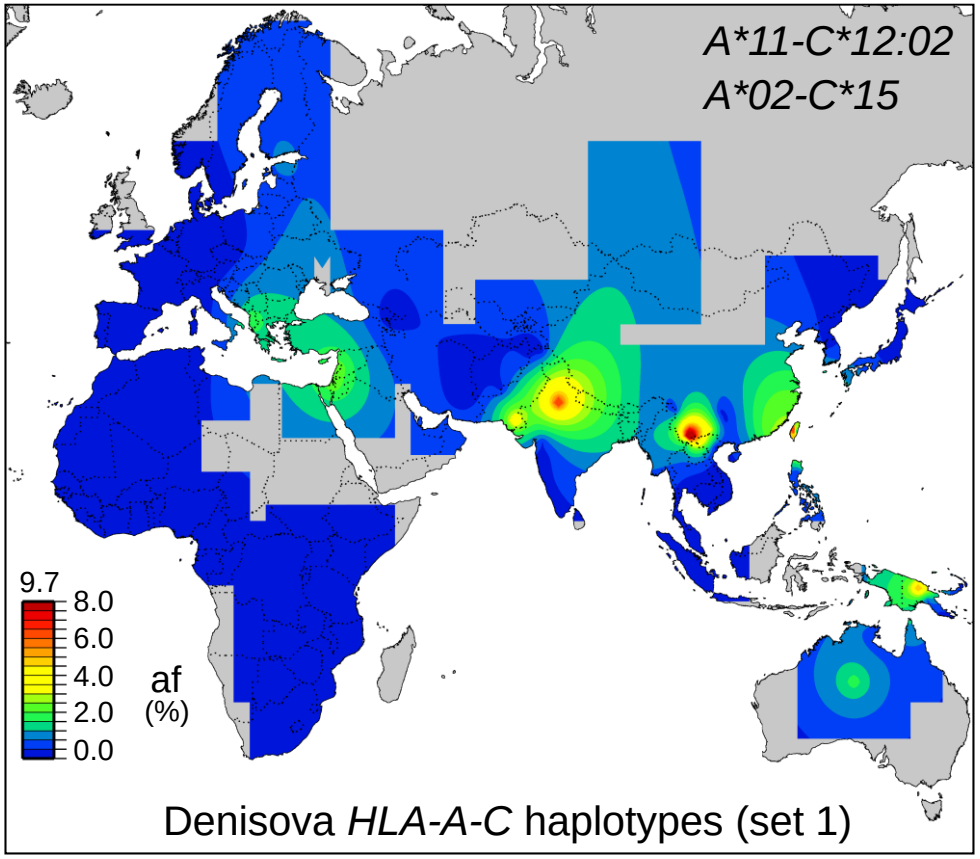
	2	39%	43	B*35:63[¶]	0	B*53	9
HLA-C	1	33%	30	C*12:02:02	0	C*06	7
	2	19%	16	C*15:02/05/17 [§]	1	C*02	5

She carried all four epitopes that are ligands for variable NK cell receptors: A3/11, Bw4, C1, and C2.

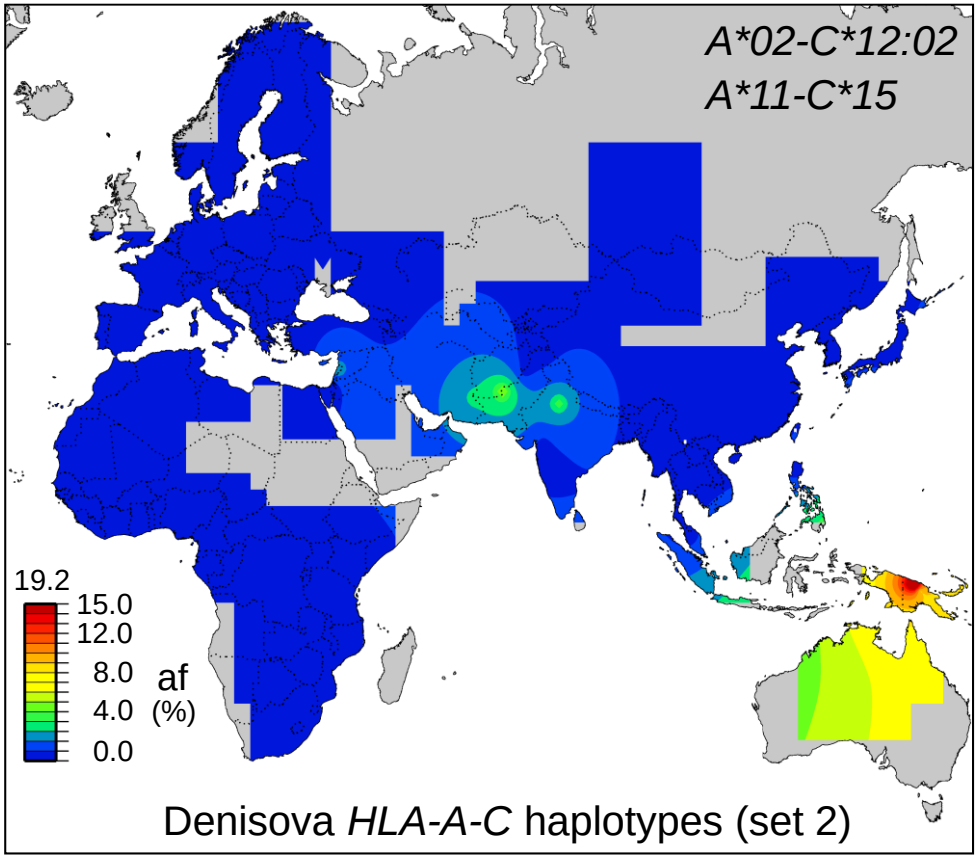
Denisovan *HLA class I*							
Allele				Closest modern type		Next best type	
Locus	#	Coverage	Reads (#)	Name	Differences	Name	Differences
HLA-A	1	15%	15	A*02:01/03/07/48	0	A*68	7
	2	21%	17	A*11:01/53	0	A*03/*30	4
HLA-B	1	34%	35	B*15:58	3	B*46	5
	2	39%	43	B*35:63¶	0	B*53	9
HLA-C	1	33%	30	C*12:02:02	0	C*06	7
	2	19%	16	C*15:02/05/17 §	1	C*02	5

The HLA-A to *HLA-C* haplotype

All possible Denisovan *HLA-A/C* haplotypes are absent from Africa and present in Asia

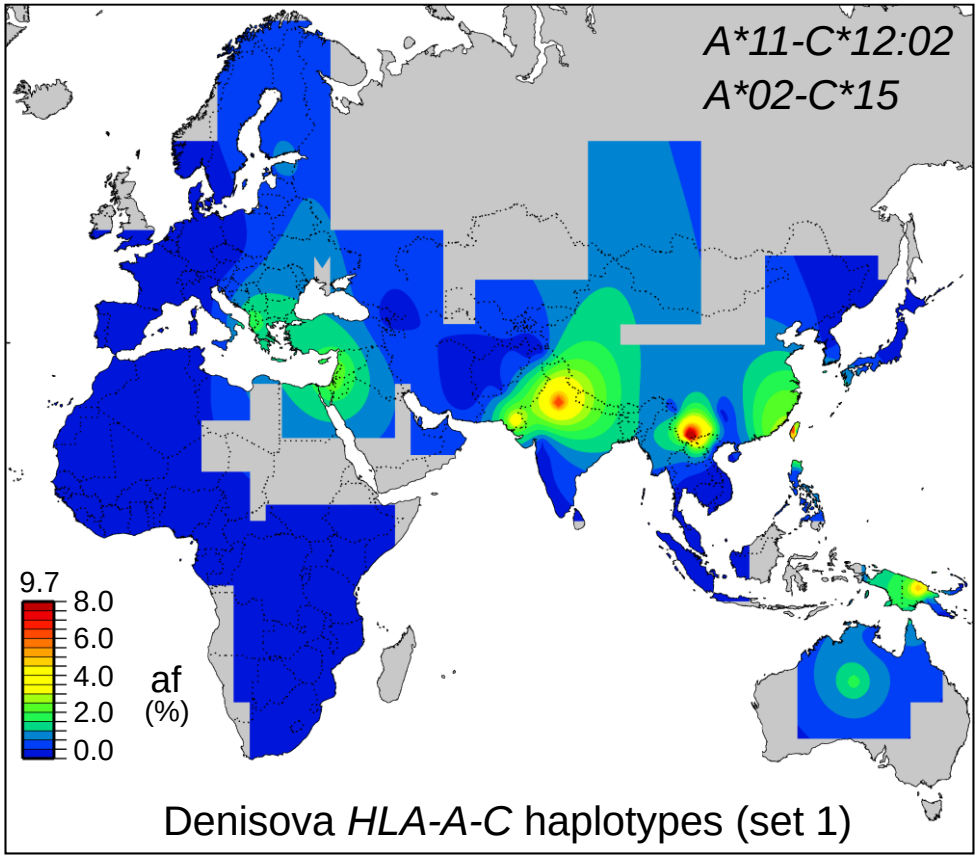


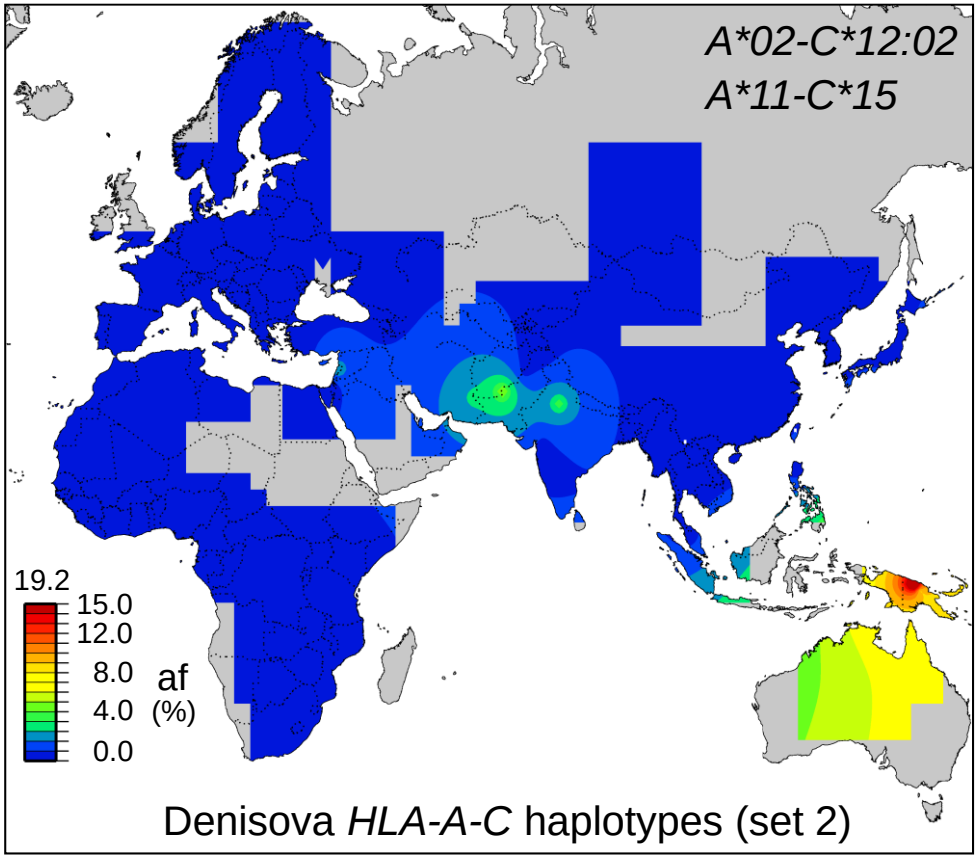
Denisova *HLA-A-C* haplotypes (set 1)



Denisova *HLA-A-C* haplotypes (set 2)

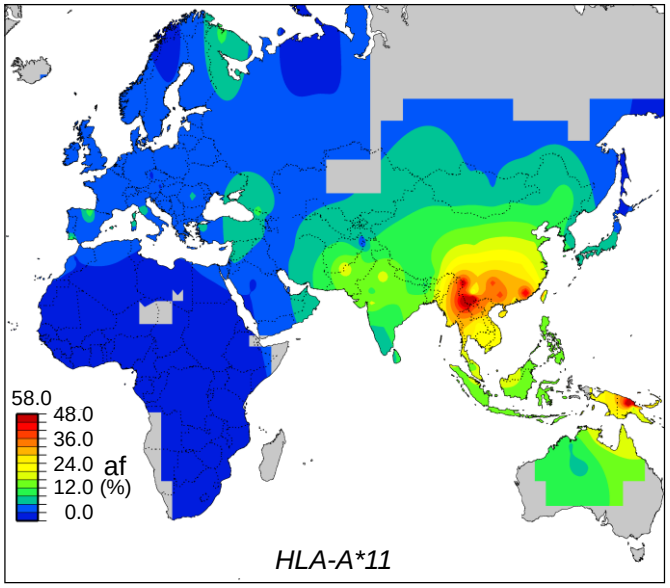
All possible Denisovan *HLA-A/C* haplotypes are absent from Africa and present in Asia

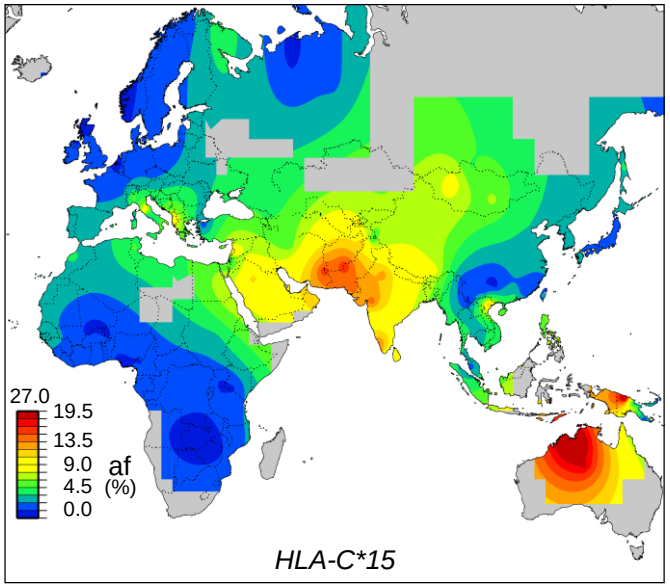


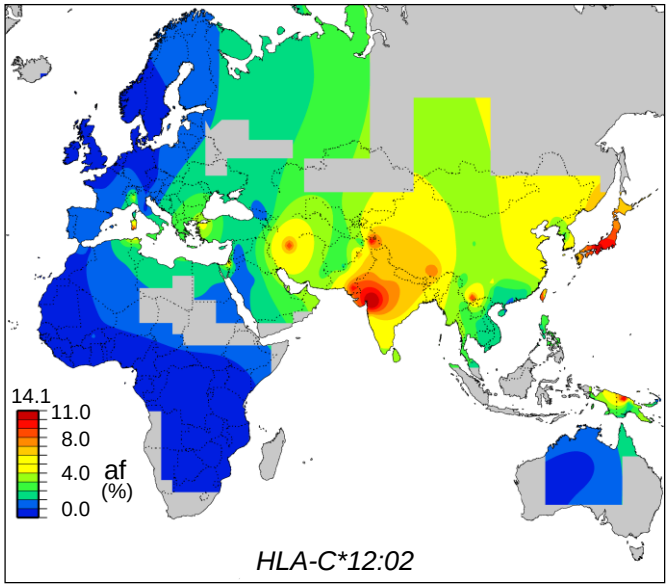


Modern humans acquired these haplotypes from archaic humans

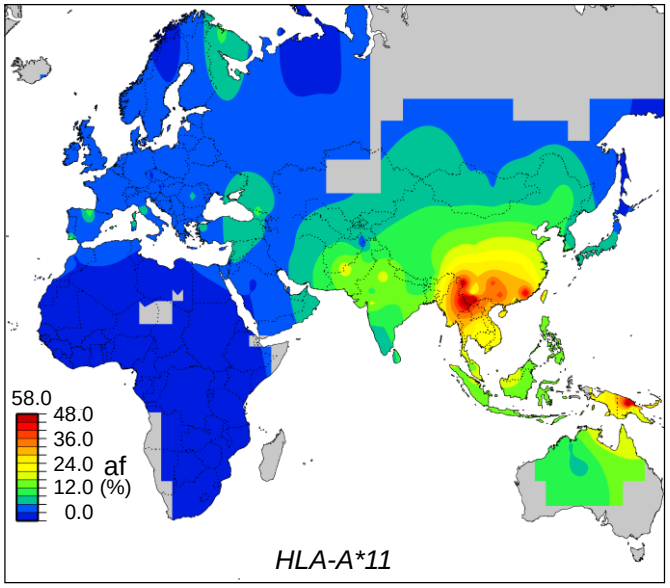
Presence of Denisovan Alleles in Asia but not Africa

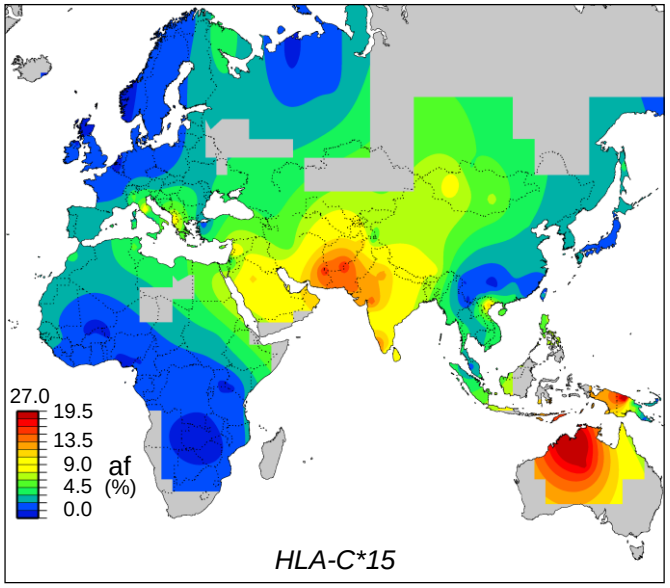


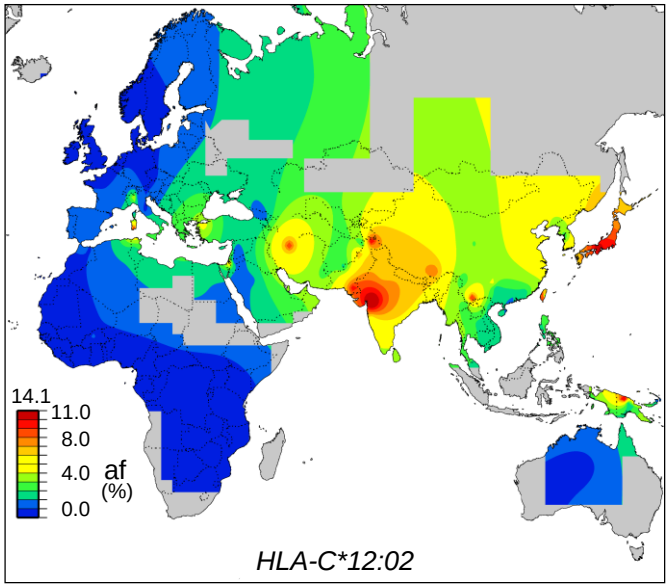




Presence of Denisovan Alleles in Asia but not Africa

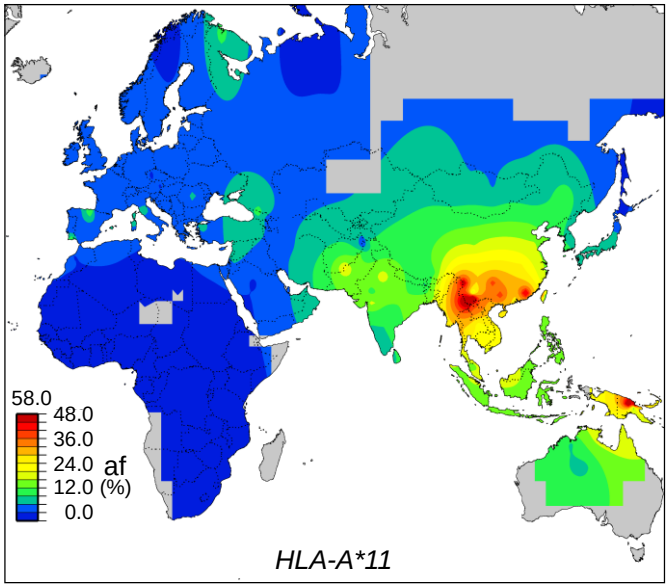


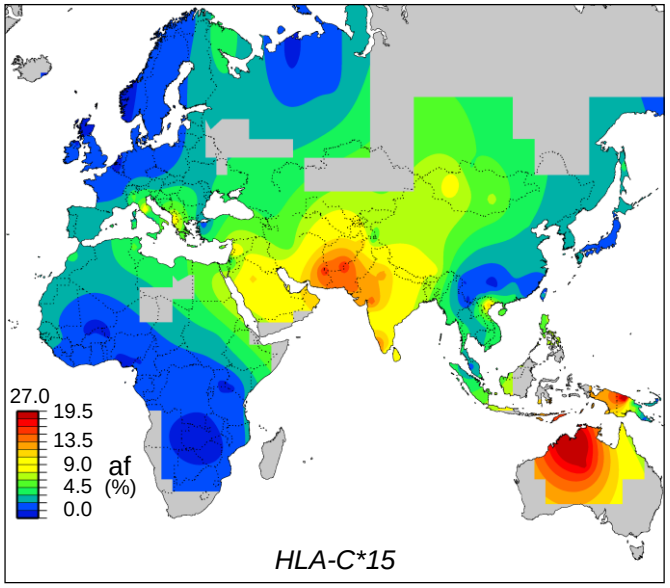


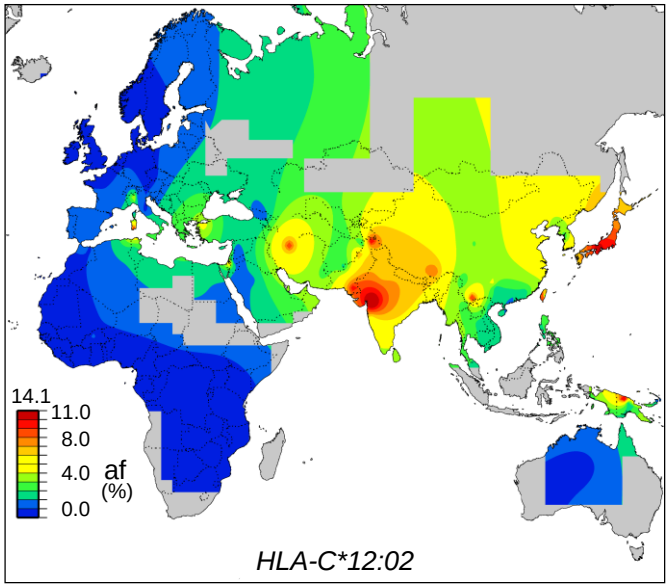


These three alleles were passed from archaic to modern humans.

Presence of Denisovan Alleles in Asia but not Africa



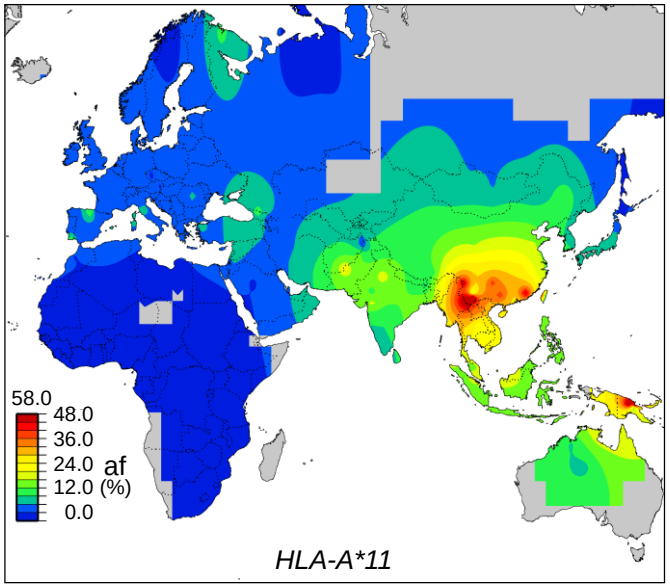


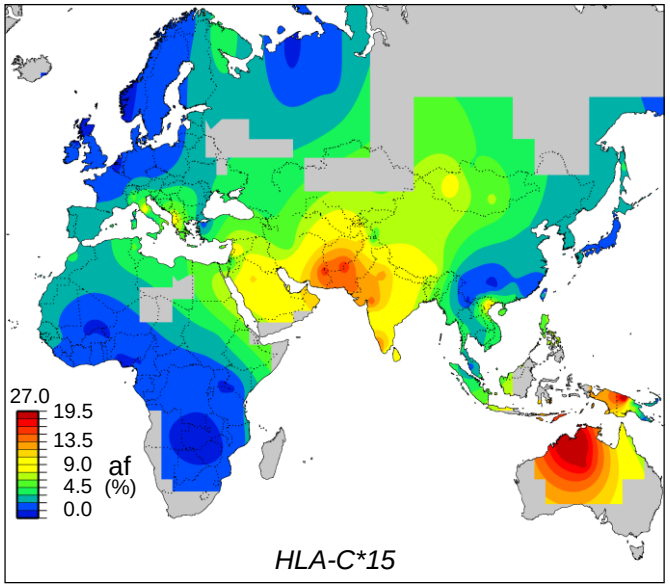


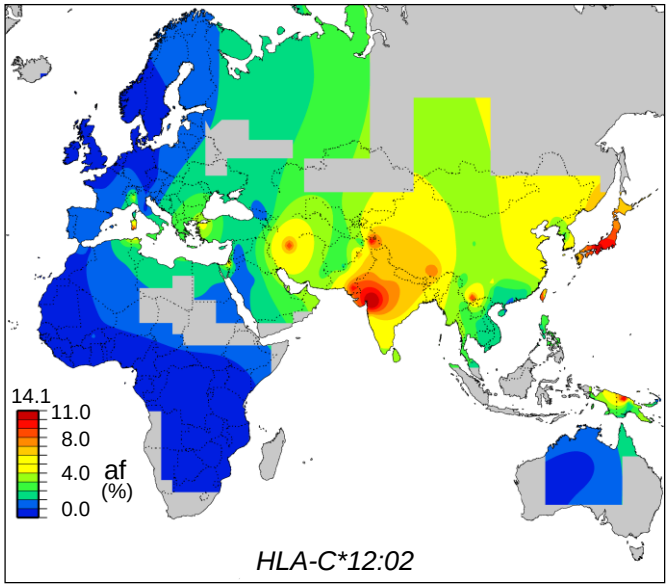
These three alleles were passed from archaic to modern humans.

Their frequencies in modern humans exceed the neutral estimates.

Presence of Denisovan Alleles in Asia but not Africa





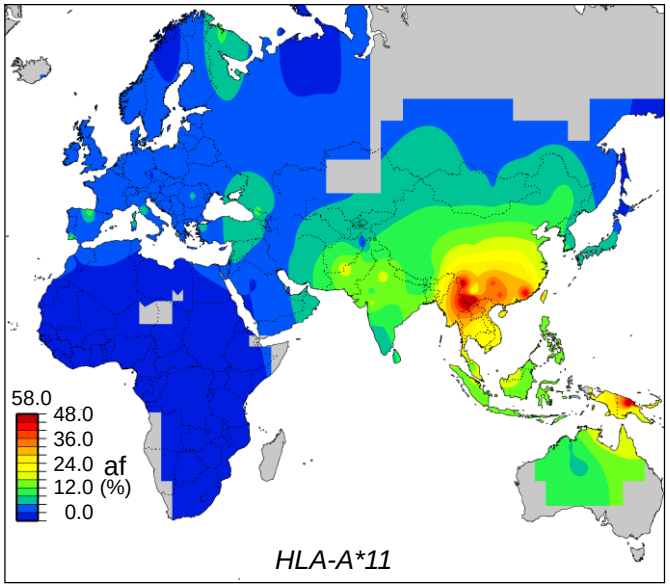


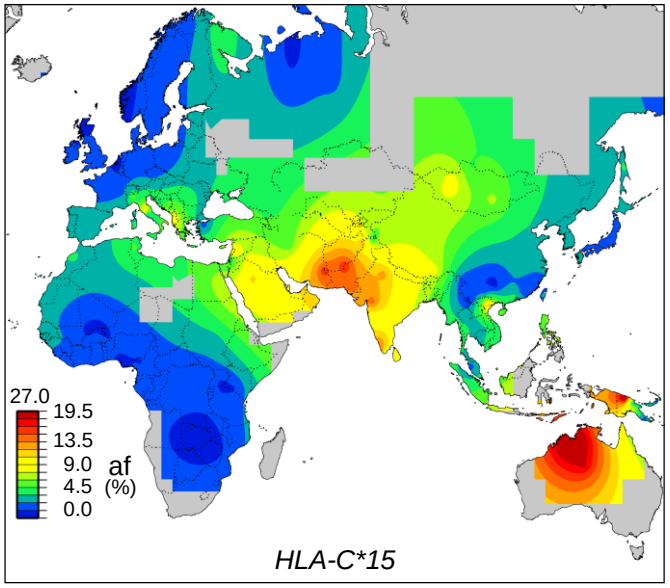
These three alleles were passed from archaic to modern humans.

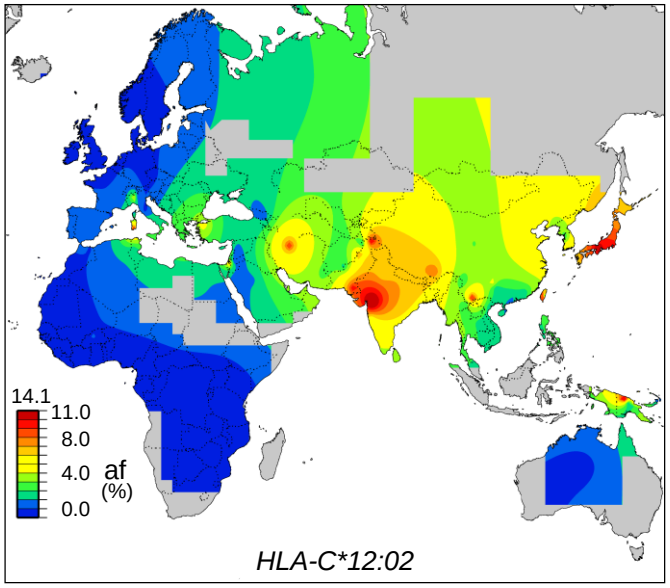
Their frequencies in modern humans exceed the neutral estimates.

On acquisition by modern humans they were subject to selection.

Presence of Denisovan Alleles in Asia but not Africa







The two Denisovan HLA-C alleles are those associated with HLA-B*73

HLA typing of the Neandertal woman.

Neandertal *HLA class I*							
Allele				Closest modern type		Next best type	
Locus	#	Coverage	Reads (#)	Name	Differences	Name	Differences
HLA-A	1	30%	40	A*02 [not :05]	0	A*68	14
	2	16%	16	A*26/*66	0	A*34	2
HLA-B	1	28%	34	B*07:02/03/06 §	0	B*48	2
	2	32%	43	B*51:01/08	0	B*52/*78	2
HLA-C	1	35%	52	C*07:02 §	0	C*08/*18	46
	2	25%	31	C*16:02 §	0	C*05	9

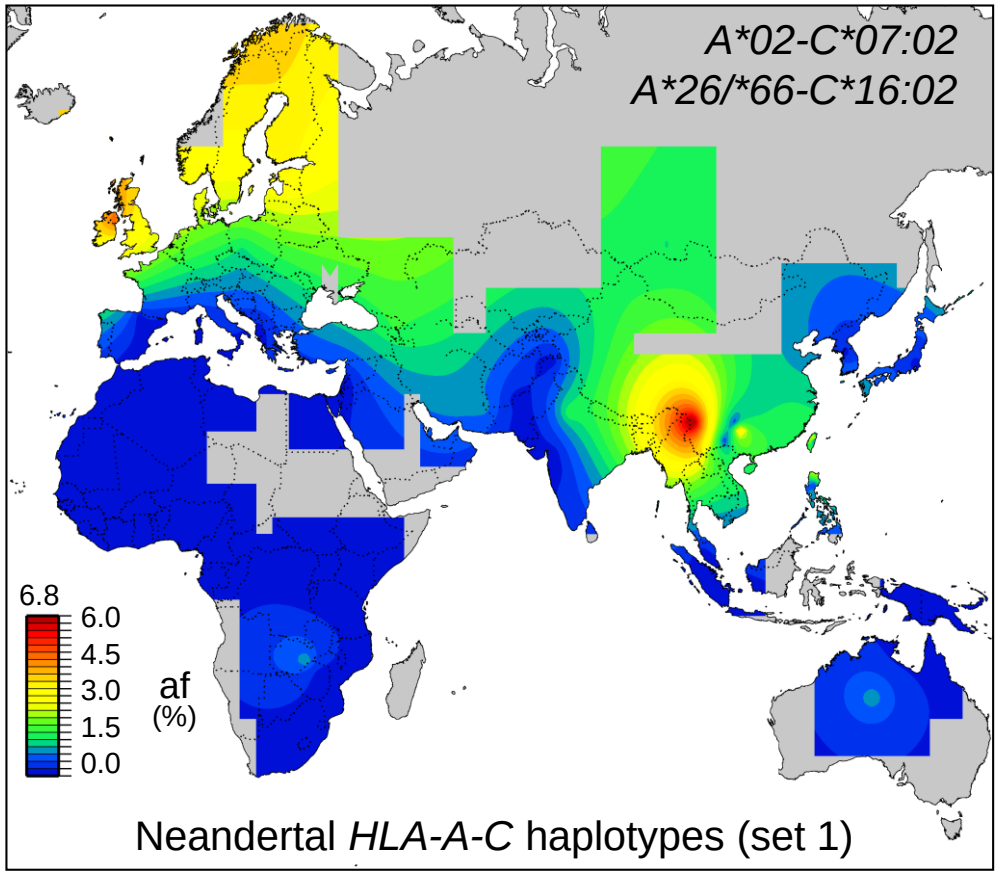
She shares all six *HLA-A, -B, -C* alleles with modern humans

Neandertal *HLA class I*							
Allele				Closest modern type		Next best type	
Locus	#	Coverage	Reads (#)	Name	Differences	Name	Differences
HLA-A	1	30%	40	A*02 [not :05]	0	A*68	14
	2	16%	16	A*26/*66	0	A*34	2
HLA-B	1	28%	34	B*07:02/03/06 §	0	B*48	2
	2	32%	43	B*51:01/08	0	B*52/*78	2
HLA-C	1	35%	52	C*07:02 §	0	C*08/*18	46
	2	25%	31	C*16:02 §	0	C*05	9

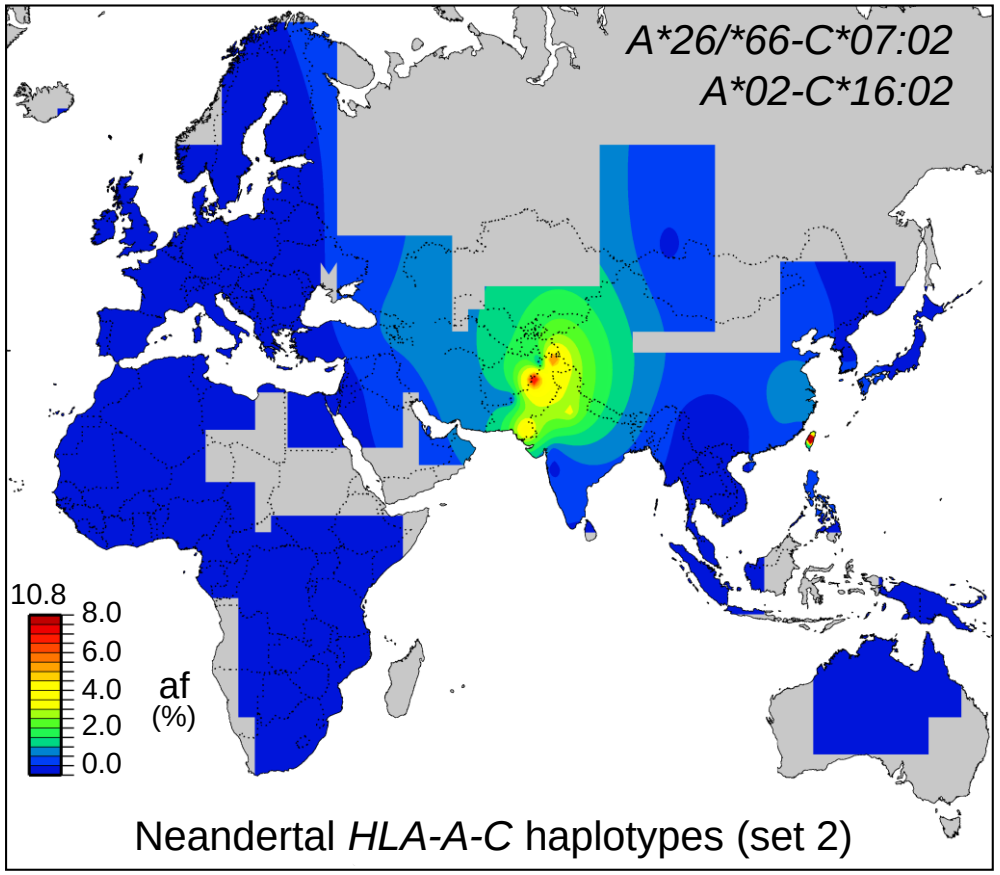
She has three of the four epitopes for NK cell receptors: C1, C2, and Bw4.

Neandertal *HLA class I*							
Allele				Closest modern type		Next best type	
Locus	#	Coverage	Reads (#)	Name	Differences	Name	Differences
HLA-A	1	30%	40	A*02 [not :05]	0	A*68	14
	2	16%	16	A*26/*66	0	A*34	2
HLA-B	1	28%	34	B*07:02/03/06 §	0	B*48	2
	2	32%	43	B*51:01/08	0	B*52/*78	2
HLA-C	1	35%	52	C*07:02 §	0	C*08/*18	46
	2	25%	31	C*16:02 §	0	C*05	9

All possible Neandertal *HLA-A/C* haplotypes are absent from Africa and present in Eurasia

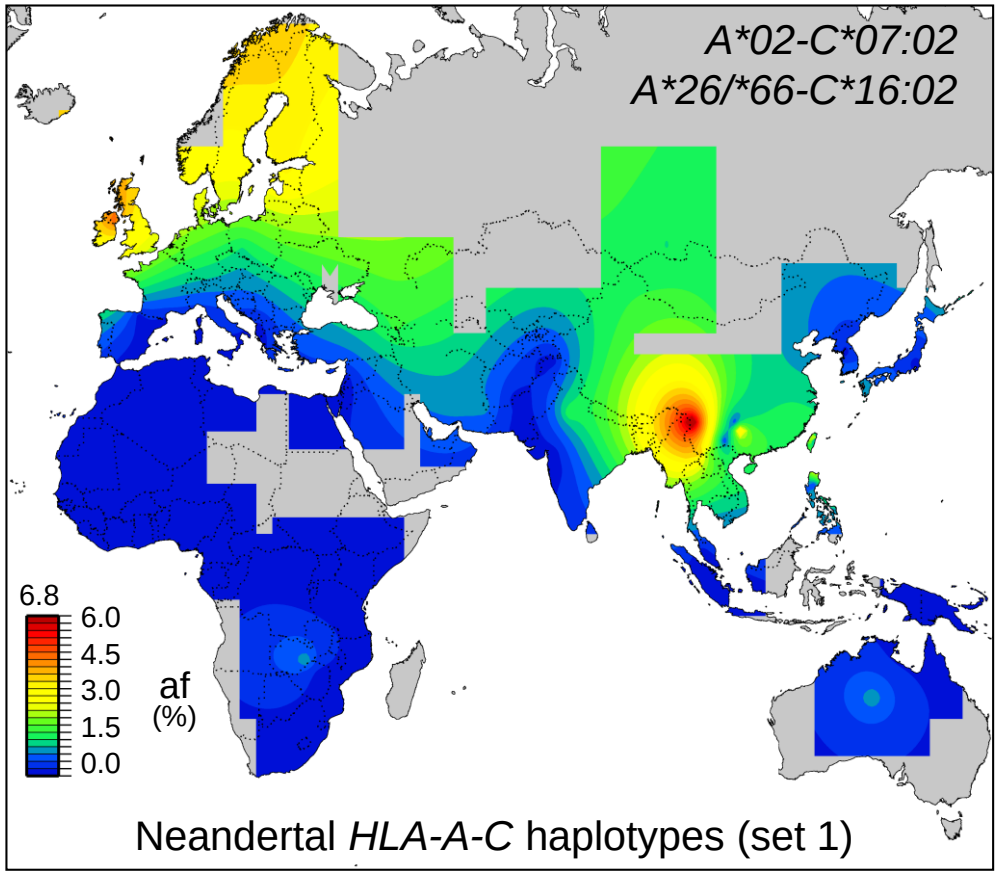


Neandertal *HLA-A-C* haplotypes (set 1)

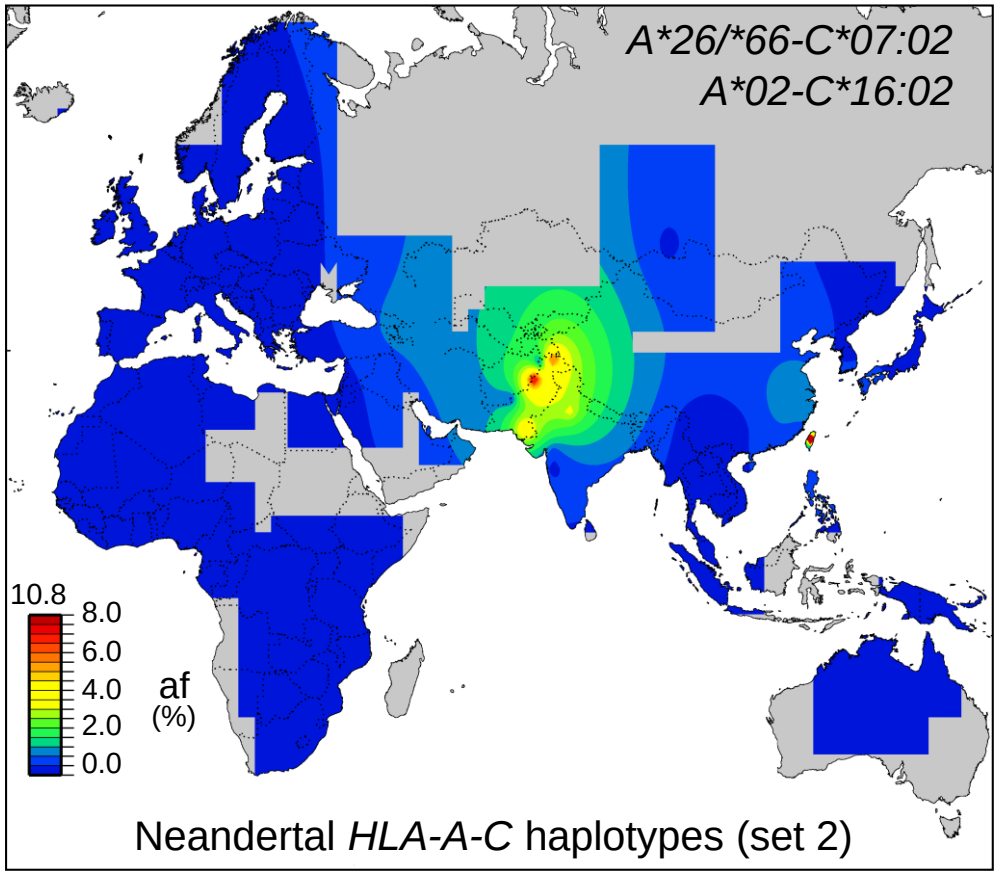


Neandertal *HLA-A-C* haplotypes (set 2)

All possible Neandertal *HLA-A/C* haplotypes are absent from Africa and present in Eurasia



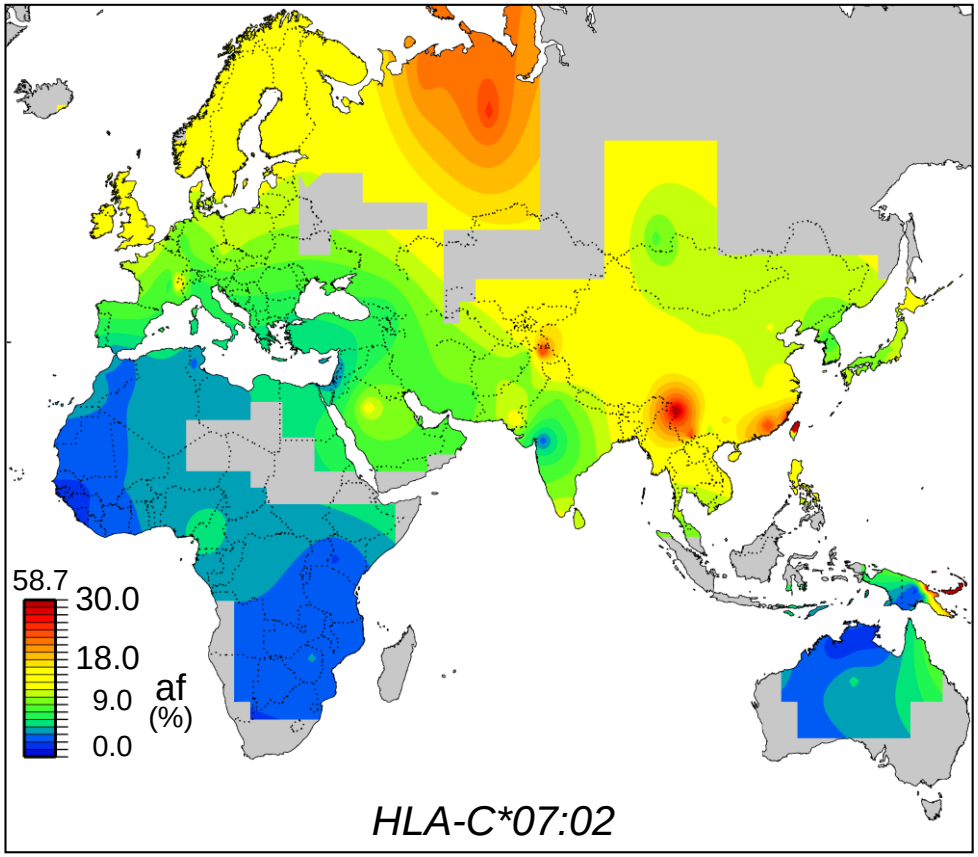
Neandertal *HLA-A-C* haplotypes (set 1)

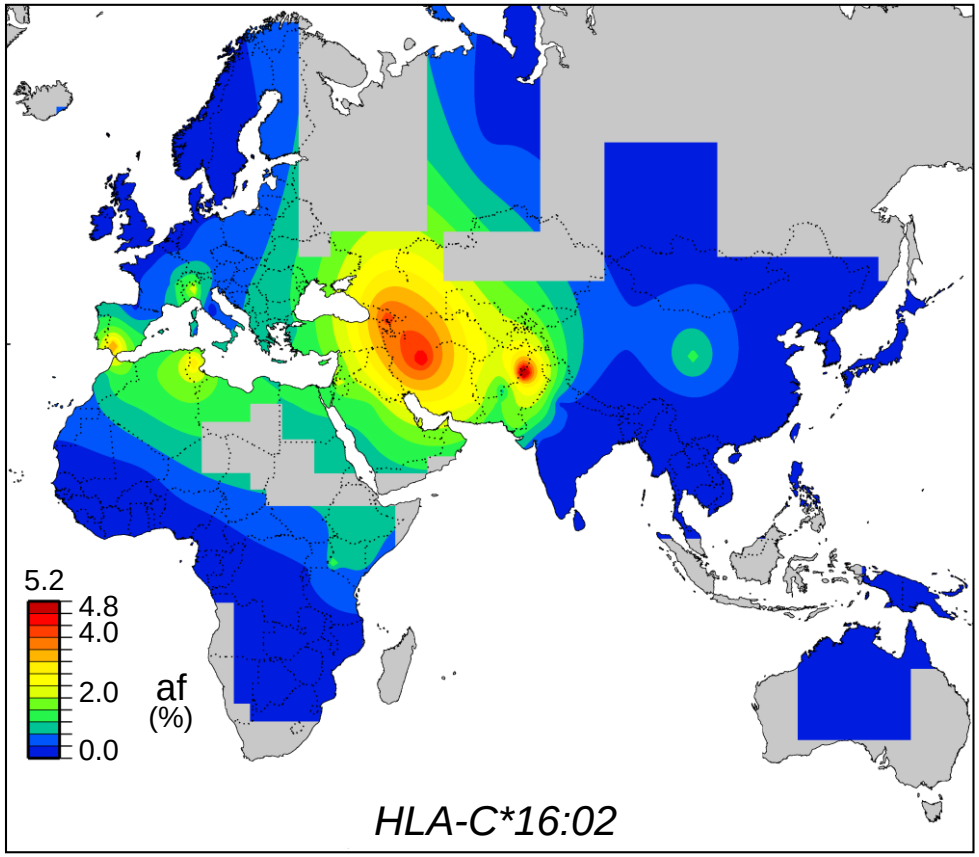


Neandertal *HLA-A-C* haplotypes (set 2)

Modern humans acquired these haplotypes from archaic humans

Modern distribution of Neandertal *HLA-C* alleles





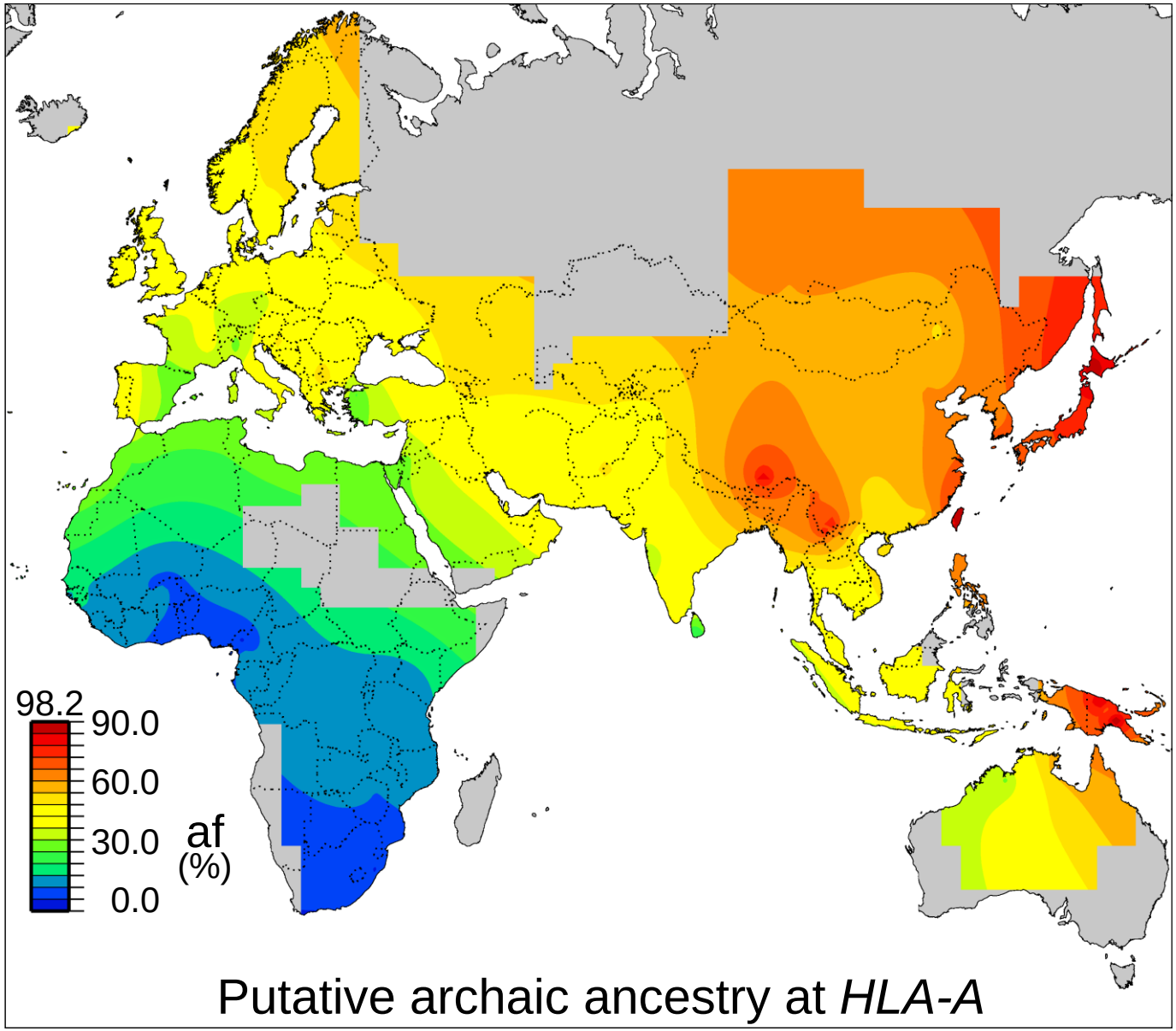
The frequencies of the Neandertal allele far exceeds those of neutral markers

On entering modern humans the Neandertal alleles were positively selected

In Today's Modern Human Population Some 50% of MHC Class I alleles Were Acquired by Social Interactions with Archaic Humans

Population	Putative archaic ancestry at *HLA-A*
African	6.7%
European	51.7%
Chinese	72.2%
Japanese	80.7%
Papua New Guinea	82.3% [65.9% - 95.3%]

Archaic contribution to HLA-A in modern Eurasians and Melanesians is >50%



Summary: I
Improving HLA diversity through population admixture

1. The contribution of archaic HLA class I to modern Eurasian and Melanesian HLA class I is much greater than the total genome estimates, pointing to selective advantage.

2. The advantage of archaic HLA class I to modern humans was to replenish lost HLA diversity and provide ready-made alleles already adapted to the local environment.

3. Adaptive introgression is unlikely to be restricted to HLA : all polymorphic gene families of the immune system and elsewhere are potential candidates for examination.

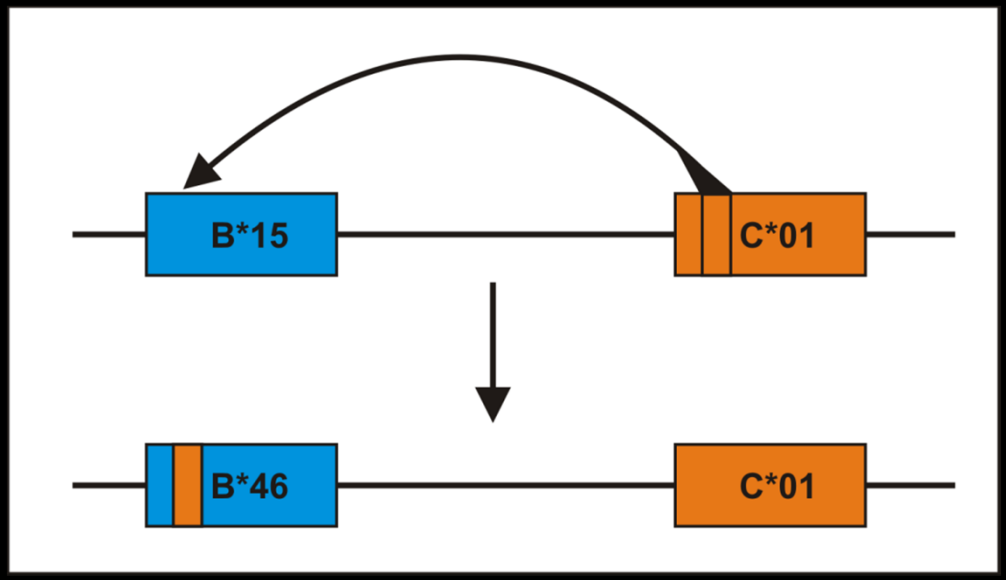
4. Population admixture is essentially another form of recombination that can introduce particularly divergent new variants with a single mating event.

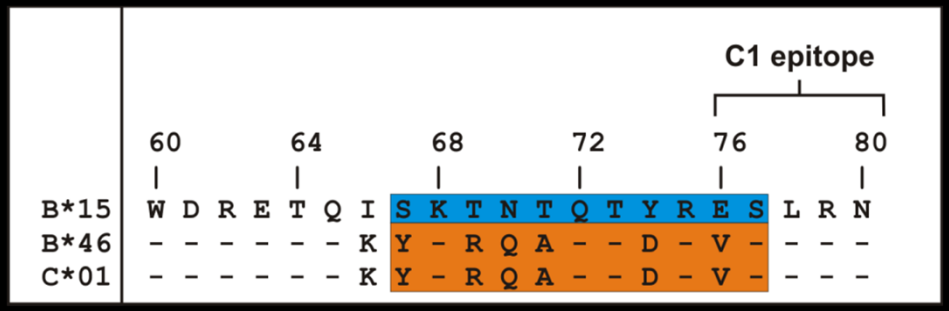
Summary: II
Improving HLA diversity through population admixture

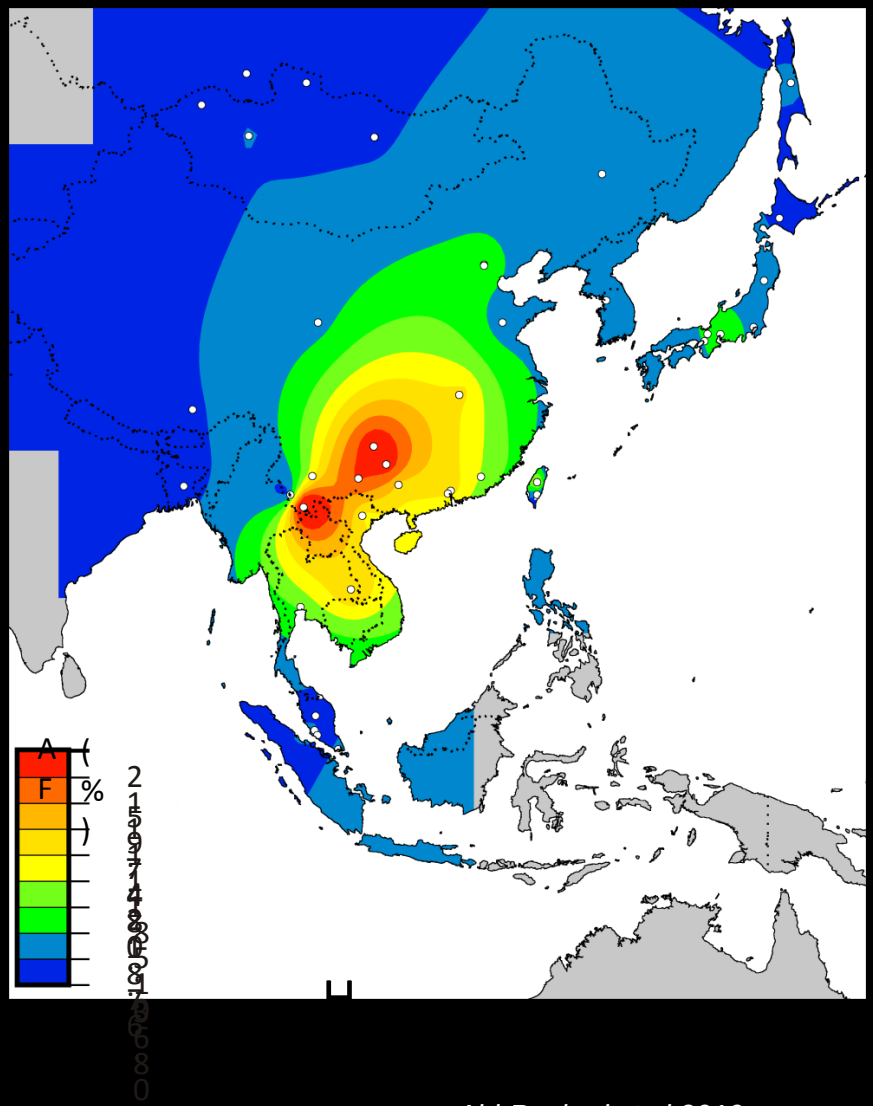
5. Acquisition of archaic HLA class I alleles may have been essential for the survival of modern humans in Eurasia.

6. The Neandertals may not have gone extinct but eventually became assimilated by a much larger population of Moderns.

Gene conversion between HLA-C and HLA-B formed C1-bearing HLA-B*46 which was selected and has spread to reach high frequencies in South East Asian populations

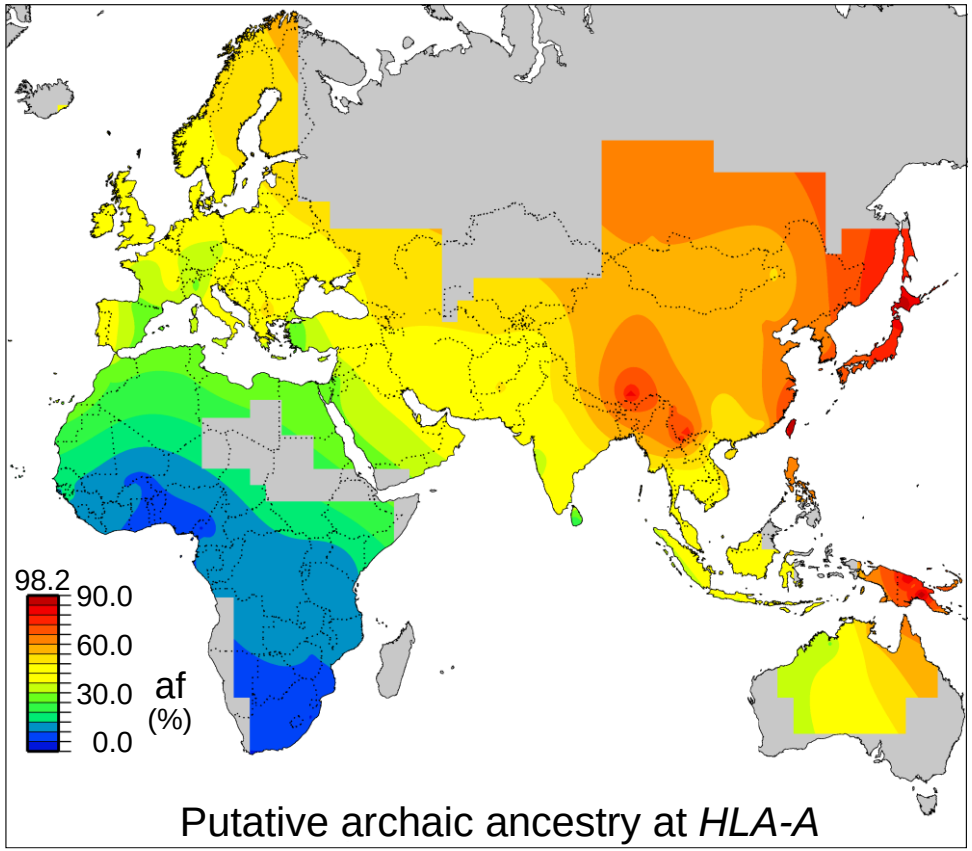




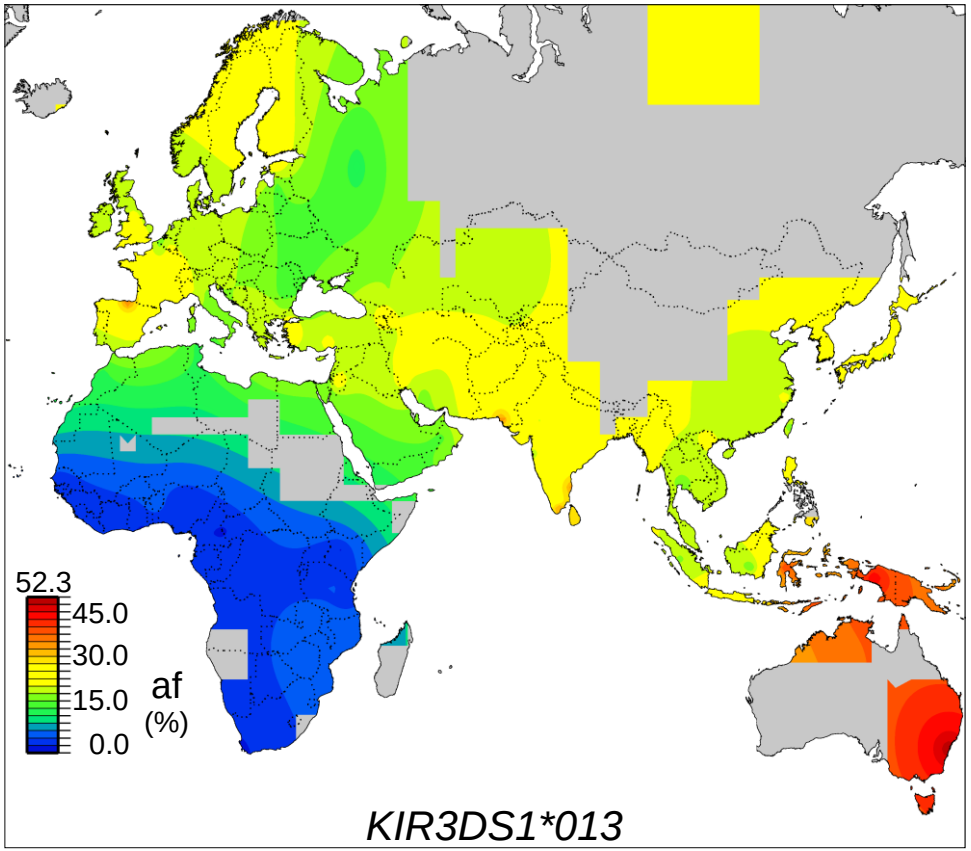


Abi-Rached et al 2010
PLoS Genetics

*KIR3DS1*013* is also a candidate for adaptive introgression



Putative archaic ancestry at *HLA-A*



*KIR3DS1*013*