How archaics shaped the modern immune system

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Outline

- Why the immune system is sensitive to archaic introgression.
- Archaic MHC alleles
- The OAS1 innate immunity locus
- STAT2

The immune system

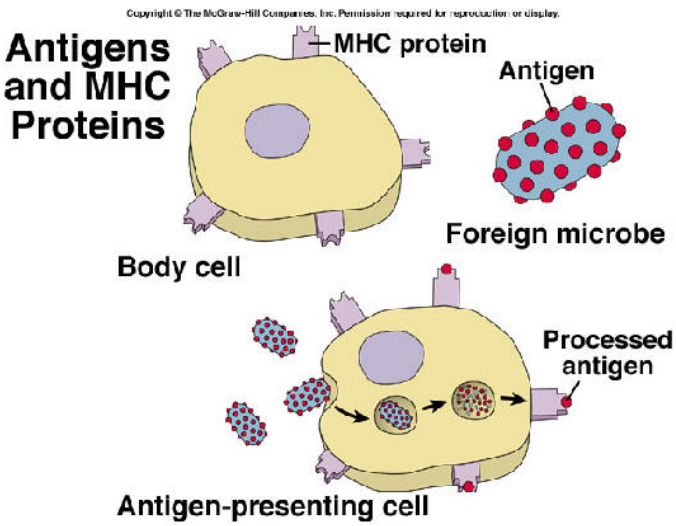
- innate immune system
- adaptive immune system

Innate immune system

- An old system found in plants, animals, fungi...
- Generic response to many types of pathogen.
- Inflammation is part of this system.
- No memory.

Adaptive immune system

- Only in vertebrates.
- Memorizes the proteins of your body.
- Attacks foreign proteins.
- MHC (major histocompatibility complex) aka HLA (human leukocyte antigen) system.



MHC (aka HLA) loci have lots of variation

- MHC loci are among the most variable in the human genome.
- HLA-A has 1000 known alleles; HLA-B has 1600; HLA-DRB1 has 870.
- Many human HLA alleles are more similar to chimpanzee alleles than to other human alleles—deep gene trees.
- Why?

Why MHC loci are so variable

- MHC proteins bind to foreign proteins and target them for destruction.
- The more MHC alleles you express, the more pathogens you can recognize.
- Selection favors heterozygotes at MHC.
- This favors rare alleles, because rare alleles are usually heterozygous. (If an allele is rare, you are unlikely to have 2 copies.)
- Selection for rarity increases variation.

Why archaic HLA alleles are likely to introgress

- Rare allele advantage favors introgressed alleles.
- Invading modern population may have lost genetic diversity because of reduced population size. This would exaggerate benefit of novel HLA alleles.
- Invaded archaic population may have evolved adaptations to local pathogens.

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HLA alleles from archaics

- Several modern HLA alleles are shared with archaics.
- This is weak evidence, because we also share with chimps and gorillas.
- But there is better evidence . . .

HLA-B allele *73.01

- Most similar to chimp and gorilla HLA-B alleles.
- Separated from other HLA-B alleles $\sim$16 my ago.
- Other HLA-B lineages have lots of variation, yet *73.01 has little.
- Ancient divergence + modern homogeneity $\Rightarrow$ archaic admixture.
- In addition, consider LD. . .

(Abi-Rached et al 2011)

B*73* individuals					
Geographic region	N	Associated *HLA-C* alleles (%)			
		*C*15*		Not *C*15*	
		15:05	not *15:05*	*12:02*	not *12:02*
Europe	2,677	98.4	0.3	0.4	0.9
Europe*	2,907	98.5	0.3	0.3	0.9
Africa	39	100	0.0	0.0	0.0
Africa##	90	97.8	2.2	0.0	0.0
W Asia	128	89.8	5.5	0.8	3.9
N/S/E Asia	53	92.5	5.7	1.9	0.0
Other	498	99.0	0.0	0.4	0.6
Total	3,676	98.2	0.5	0.4	0.9

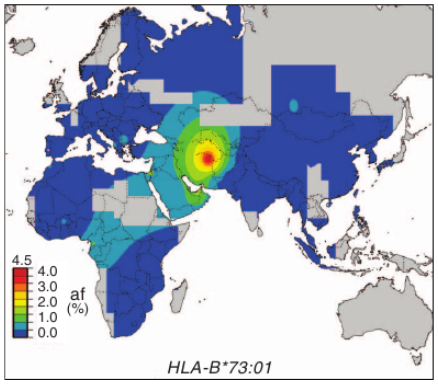
HLA-B*73.01 associated with HLA-C*15. LD across ∼1.3 Mb.

Long LD block ⇒ short time in human population.

HLA-C*15 is in Denisovan genome.

Suggests archaic introgression.
(Abi-Rached et al 2011)

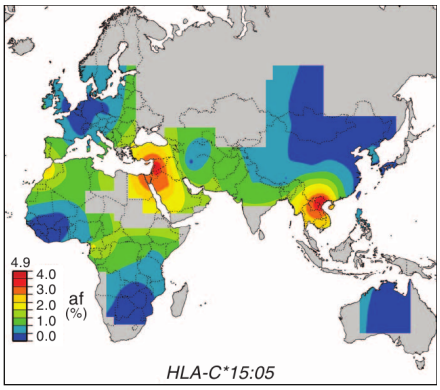
Distribution of HLA-B*73:01 allele



Common in Central Eurasia, rare in Africa.

Consistent with archaic introgression.
(Abi-Rached et al 2011)

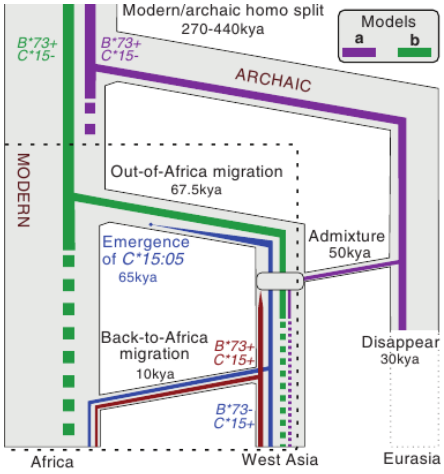
Distribution of HLA-C*15:05 allele



Common in Eurasia, rare in Africa.

Consistent with archaic introgression.
(Abi-Rached et al 2011)

History of B*73:01-C*15 HLA haplotype



Other HLA alleles

There are other HLA alleles with similar stories.

Abi-Rached et al (2011) estimate that $> 50\%$ of Eurasian HLA alleles came from archaics.

Archaics contributed a lot to the adaptive immune systems of modern humans.

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OAS1 innate immunity locus

- two forms of gene in Melanesia:
- one shared with rest of world
- one only in Melanesia

Neanderthal and Denisova haplotypes at OAS1

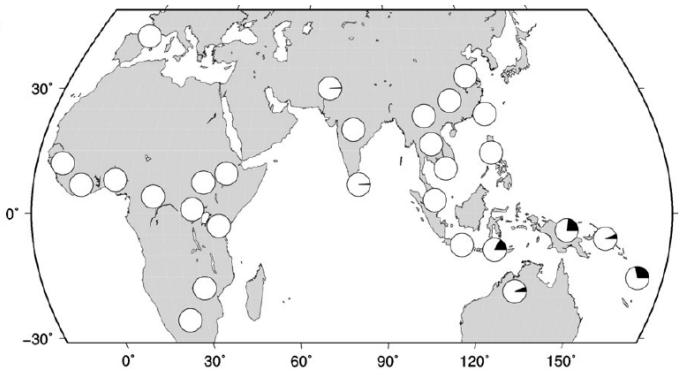
Haplotypes[a]	Base Position[b]																Populations[c]						
	6900	6922	6935	6980	7193	7202	7209	7216	7237	7267	7409	7442	7494	7565	7663	7688	7708	Africans			Non-Africans		
Ancestral	A	C	C	C	G	C	G	A	G	AT	C	G	C	C	T	G	A						
Neandertal	.	T	.	T	.	.	.	.	.	.	.	.	.	.	A	N	N	B	M	S	P	H	F
Denisova	.	.	.	.	.	.	A	.	C	.	.	A	.	N	A	N	.						
R	.	T	.	T	.	.	.	.	.	.	.	.	.	.	A	A	.	0	0	0	0	8	6
K	G	.	T	.	.	.	.	.	.	.	.	.	G	.	.	.	G	0	1	2	0	0	0
D	.	.	.	.	.	.	A	.	C	–[d]	.	A	.	.	A	A	.	0	0	0	7	0	0
P	.	.	.	.	.	.	A	.	C	.	.	A	.	.	A	A	.	0	0	0	11	0	0
S	.	T	.	T	.	.	A	G	C	.	T	A	.	T	A	A	.	1	0	3	0	0	0
F	.	T	.	T	.	.	A	.	C	.	.	A	.	.	A	A	.	17	20	10	0	0	0
A	.	T	.	T	A	.	A	.	C	.	.	A	.	.	A	A	.	12	11	5	12	21	26
H	.	T	.	T	A	T	A	.	C	.	.	A	.	.	A	A	.	0	0	0	0	3	0

Populations: B, Biaka; M, Mandenka; S, San; P, Papuan; H, Han; F, French Basque.

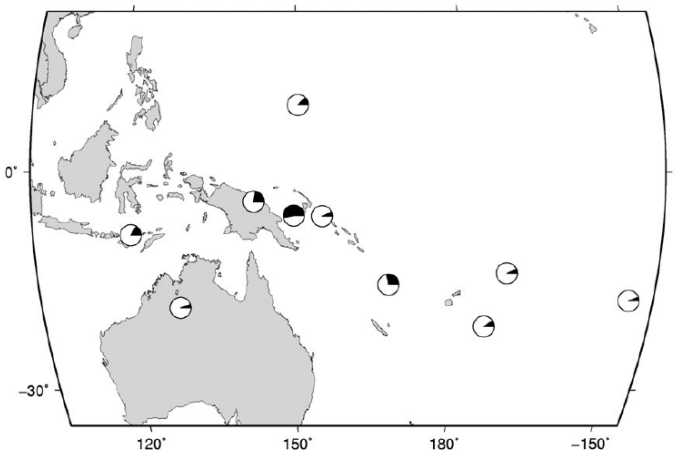
(Mendez et al. 2013)

Reference sequence, R, is Neanderthal; Melanesian sequence, P, is Denisovan.

Worldwide frequency of Melanesian OAS1 allele



Melanesian OAS1 allele w/i Melanesia



Melanesian OAS1 allele is old yet young

- The 2 alleles differ at many nucleotide sites ⇒ separation time ∼3.4 my.
- Long (90 kb) LD block ⇒ they've been together only ∼25 ky
- Melanesian allele matches that in Denisovan hominin skeleton.

⇒ archaic admixture into Melanesia

Another look at the R haplotype

Haplotypes[a]	Base Position[b]																Populations[c]						
	6900	6922	6935	6980	7193	7202	7209	7216	7237	7267	7409	7442	7494	7565	7663	7688	7708	Africans			Non-Africans		
Ancestral	A	C	C	C	G	C	G	A	G	AT	C	G	C	C	T	G	A						
Neandertal	.	T	.	T	.	.	.	.	.	.	.	.	.	.	A	N	N	B	M	S	P	H	F
Denisova	.	.	.	.	.	.	A	.	C	.	.	A	.	N	A	N	.						
R	.	T	.	T	.	.	.	.	.	.	.	.	.	.	A	A	.	0	0	0	0	8	6
K	G	.	T	.	.	.	.	.	.	.	.	.	G	.	.	.	G	0	1	2	0	0	0
D	.	.	.	.	.	.	A	.	C	–[d]	.	A	.	.	A	A	.	0	0	0	7	0	0
P	.	.	.	.	.	.	A	.	C	.	.	A	.	.	A	A	.	0	0	0	11	0	0
S	.	T	.	T	.	.	A	G	C	.	T	A	.	T	A	A	.	1	0	3	0	0	0
F	.	T	.	T	.	.	A	.	C	.	.	A	.	.	A	A	.	17	20	10	0	0	0
A	.	T	.	T	A	.	A	.	C	.	.	A	.	.	A	A	.	12	11	5	12	21	26
H	.	T	.	T	A	T	A	.	C	.	.	A	.	.	A	A	.	0	0	0	0	3	0

Populations: B, Biaka; M, Mandenka; S, San; P, Papuan; H, Han; F, French Basque.

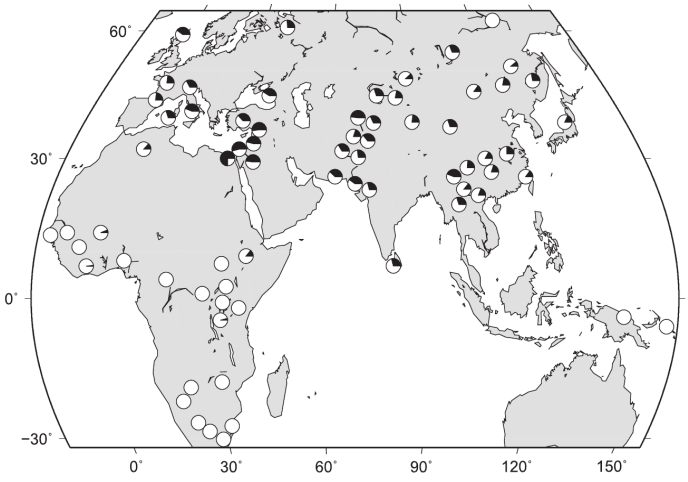
(Mendez et al. 2013)

Introgressed from Neanderthal.

Extends to 2nd locus, OAS2.

Associated with sensitivity to tick-borne encephalitis.

Worldwide frequency of OAS1 R allele



Selection has favored Neanderthal OAS alleles in modern humans

Several Neanderthal-like sequences in the OAS region show evidence of positive selection. (Reduced variation within the Neanderthal haplotype across a broad region of chromosome.)

(Sams et al 2016)

Neanderthals resurrected an ancestral gene in Europeans

During translation into protein, introns must be sliced out and discarded.

In some genes, the exons may be spliced together in several ways, using "alternative splice sites."

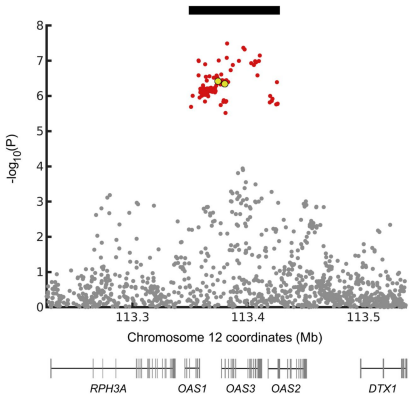
At one OAS locus, all human populations carry a particular alternative splice site, which generates an enzyme that fights viruses.

Within Eurasians, this splice site is found only on Neanderthal-like haplotypes.

Suggests that early Eurasians lost this splice site, then regained it by mating with Neanderthals.

(Sams et al 2016)

Neanderthal OAS haplotype fights Covid-19



X axis: position on chromosome 12

Y axis: association with resistance to severe Covid-19

red dots: alleles associated with resistance to Covid-19

These resistant alleles are derived from Neanderthals

OAS genes shown at bottom.

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- ▶ STAT2

STAT2, a gene involved in viral defence

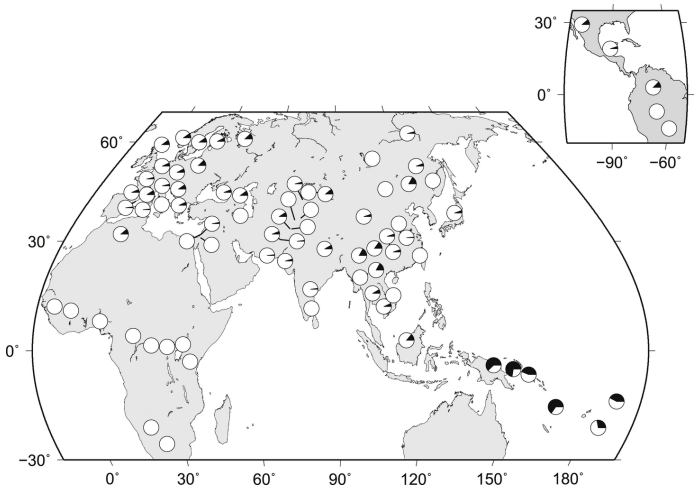
N allele, found at low frequencies throughout Eurasia—but not Africa.

N allele shared with Neanderthal.

N allele on a long LD block (260 kb)—implies introgression w/i past 92 ky.

10× as common in Melanesia—suggests selection.

Worldwide frequency of N lineage of STAT2



Summary

- Immunity genes are likely to introgress because
  1. Native population has adapted to local pathogens.
  2. Invading population may have lost diversity through bottlenecks.
  3. Selection favors rare HLA alleles.
- >50% of Eurasian HLA alleles came from Neanderthals and Denisovans.
- Neanderthals and Denisovans contributed alleles to Eurasian populations at the OAS1 innate immunity locus.
- The Melanesian allele at OAS1 diverged 3.5 my ago.
- At the STAT2 locus, Neanderthals contributed an allele that is common in Eurasia but not Africa.
- Archaic admixture had a big effect on the immune system.