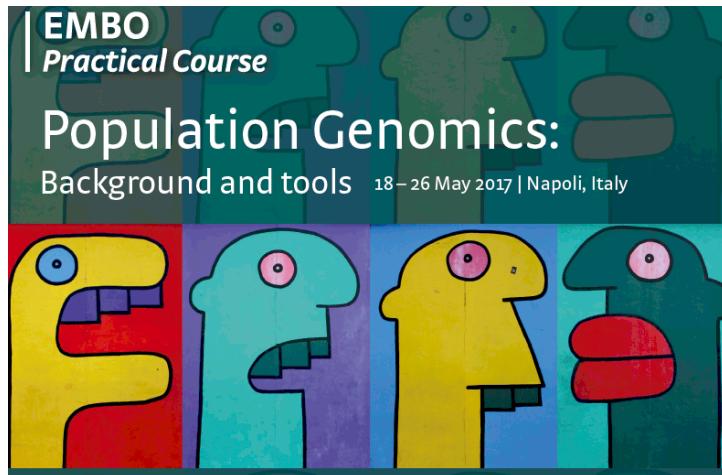


Measures of natural selection

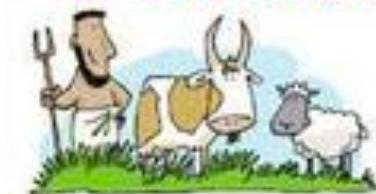
EMBO practical course 2017

Pascale Gerbault

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A SHORT HISTORY OF DNA



8000 BC
Long before the discovery of DNA, early farmers were using selective breeding to improve their crops and livestock. They kept back the best seed and offspring from their farms to begin the next generation.



1859
Charles Darwin publishes his theory of evolution through natural selection. It was only long after his death that his ideas finally became widely accepted.



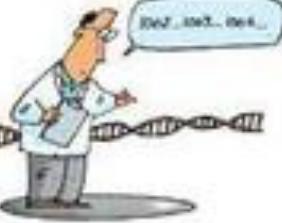
1863
Gregor Mendel, a monk in Austria, first documents hereditary traits in garden peas.

1953
James Watson and Francis Crick accurately describe the molecular structure of DNA as a double helix.

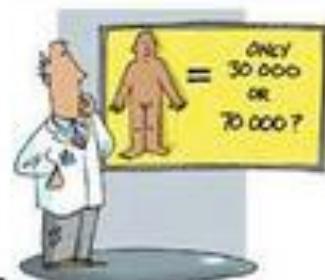
1966
The genetic code is revealed. It is established that a sequence of three nucleotide bases corresponds to each of 20 amino acids in the production of proteins. Since then a further two amino acids have been discovered.



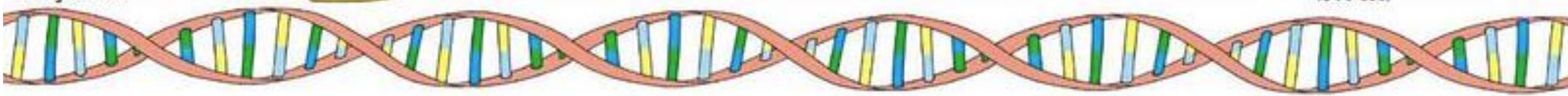
1972
The DNA composition of humans is found to be 99% similar to chimpanzees and gorillas.



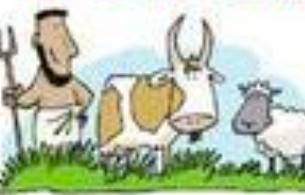
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The Human Genome Project is launched - an international collaborative effort to sequence the entire human genome.



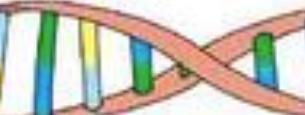
2002
The Human Genome Project is completed - revealing the location of around 30 000 human genes. This number, however, is currently being debated by scientists who suggest the number is closer to 70 000.



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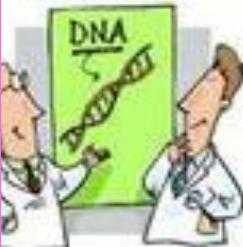


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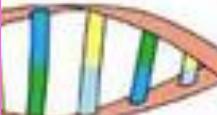
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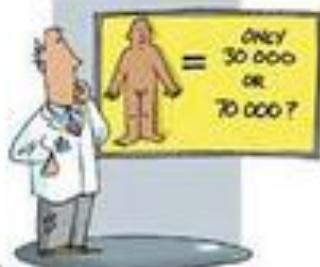
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- Why are Mendel's and Darwin's works still relevant today?
 - Examples of deliberate cross breeding...
 - => possible because most populations are genetically variable



- Darwinian concepts of selection have been rendered quantitative and measurable in real populations, thanks to methodological and technological advances.
- Evolutionary genetics contributed to the understanding of many adaptive traits, e.g. in humans lactase persistence, skin pigmentation, in mice coat color
- Approaches: (1st) phenotype hypothesised to be adaptive; (2nd) identification of underlying locus/loci
- Genomic advancements: test genomic evidence of selection on putative traits > uncovering candidate genetic regions through genome scans

What evidence is there for evolution?

- Change in allele frequencies > drift?
- Change in allele frequencies > natural selection? >> adaptation
“meaningful variation”

What evidence is there for evolution?

- Change in allele frequencies > drift?
- Change in allele frequencies > natural selection? >> adaptation
“meaningful variation”
- => selection affects the PHENOTYPE ~ genomic variation of *functional significance*
- One of the strongest selection acting on humans?

An example of ongoing natural selection that affects humans:

The evolution of drug-resistant bacteria

7:22min video on Natural selection and the bacterial resistance
<https://www.youtube.com/watch?v=7VM9YxmULuo>

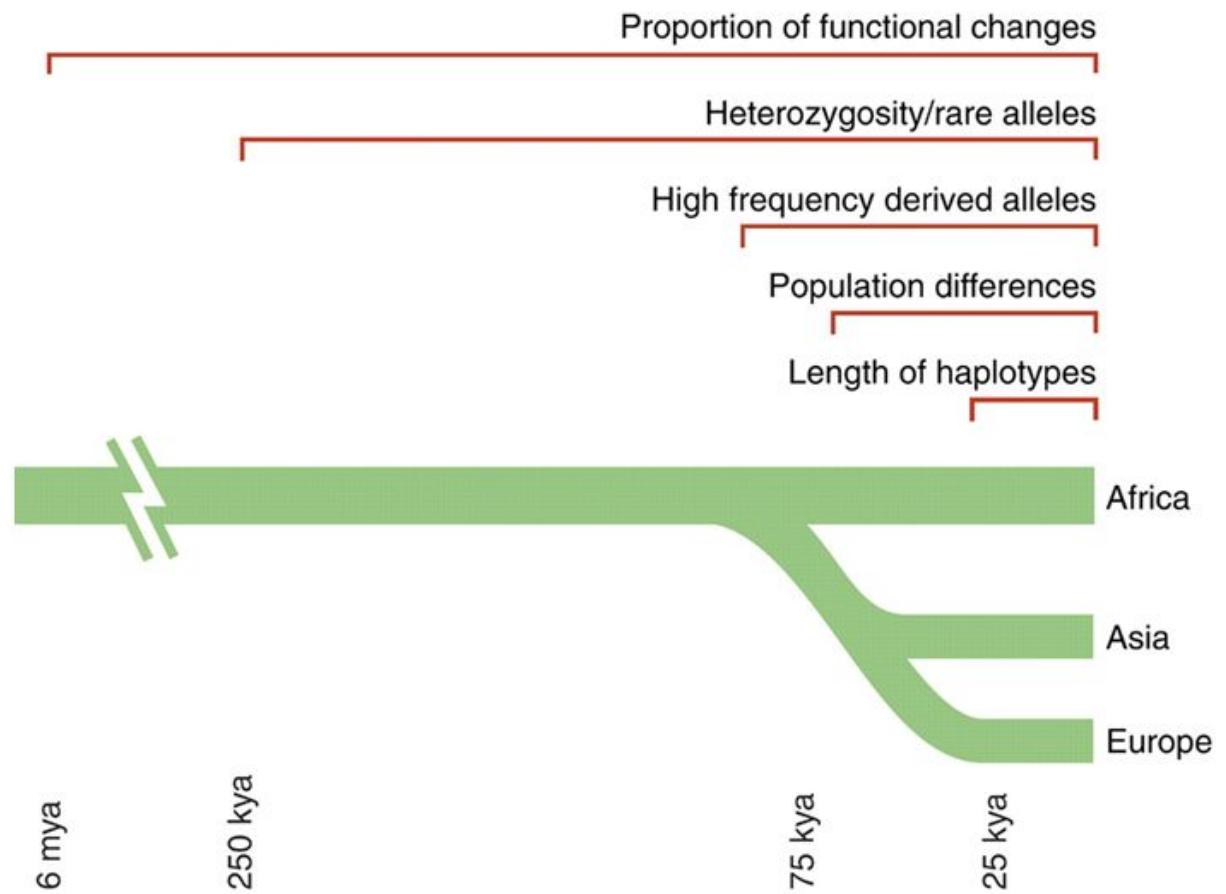
‘SELECTION’: One term, one process?

- Macro/micro evolutionary scale
- Negative, diversifying, positive selection
- Selective sweep, hard/soft sweep

Methods to infer selection

- Different methods have different power according to the time and strength of selection

Fig. 1. Time scales for the signatures of selection.

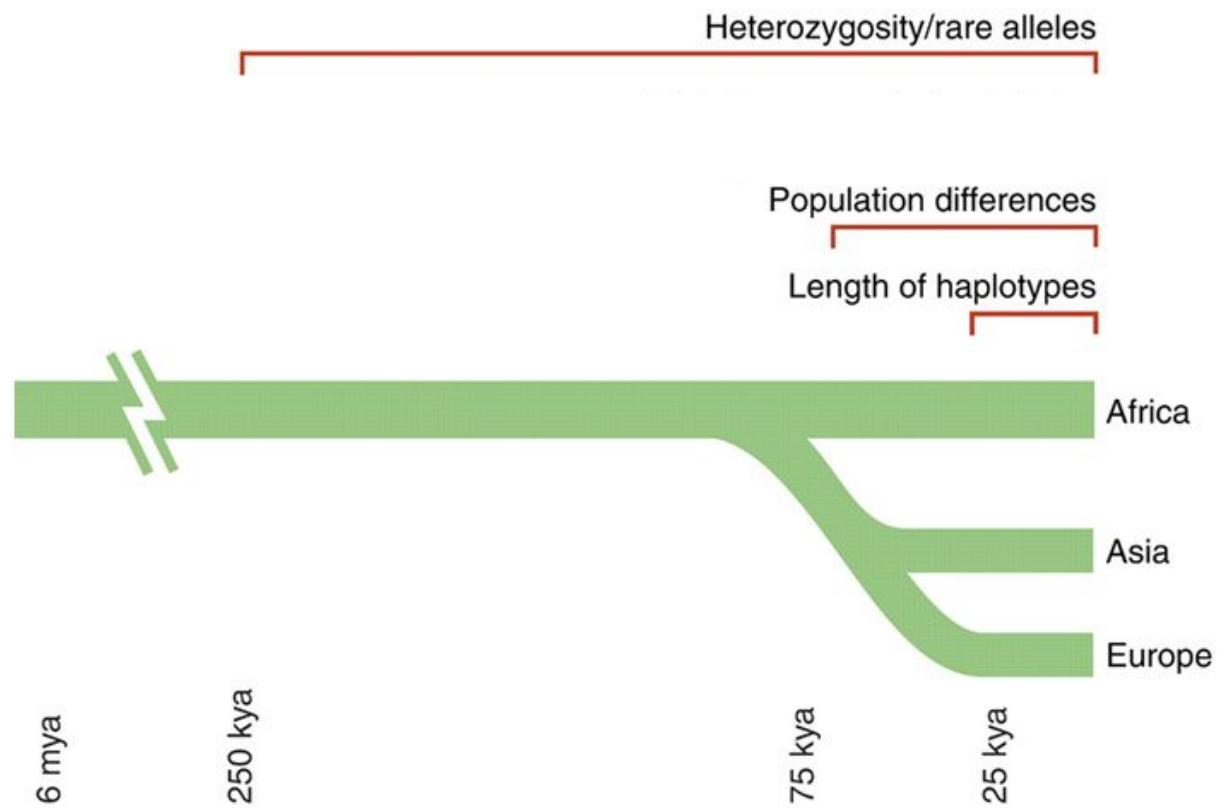


P C Sabeti et al. Science 2006;312:1614-1620

Methods to infer selection

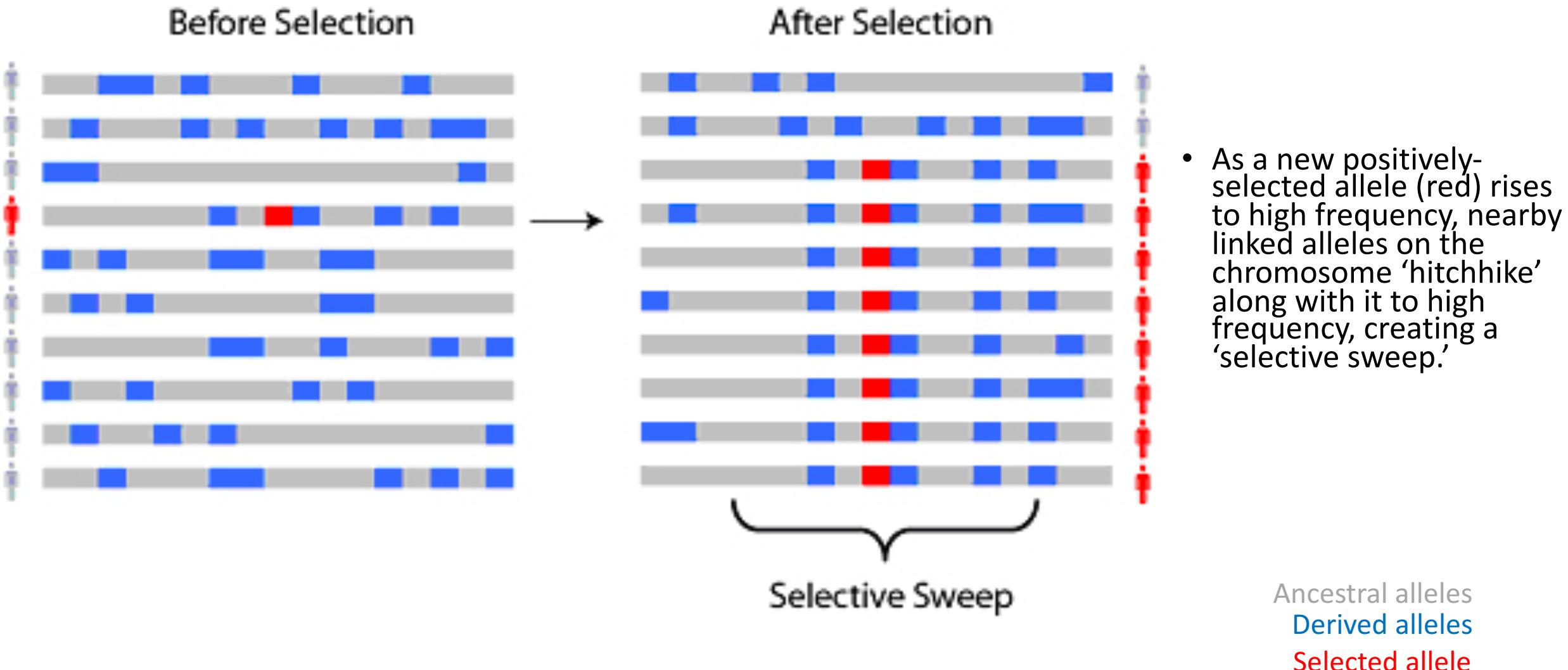
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Heterozygosity/rare alleles



Statistical Method for Testing the Neutral Mutation Hypothesis by DNA Polymorphism

Fumio Tajima

Department of Biology, Kyushu University, Fukuoka 812, Japan

Manuscript received February 13, 1989

- Tajima's D compares two estimators of genetic diversity:
the average number of nucleotide differences $\hat{\theta}_T$ and the
number of segregating sites $\hat{\theta}_W$
- If the population is at equilibrium: Tajima's D ~ 0
- Rare variants contribute little to the number of pairwise
differences
- After a selective sweep, the number of segregating sites
will be $>>$ than the average number of pairwise
differences
- Because after a selective sweep, most sequences will be
the same \rightarrow when mutations occur \Rightarrow rare
- rare mutations \rightarrow low value of the average number of
nucleotide differences in comparison to the number of
segregating sites
- If number of segregating sites $>>$ average number of
pairwise differences \Rightarrow Tajima's D < 0
- Smaller values of Tajima's D \sim positive selection... or
population expansion

$$\hat{\theta}_T = \frac{\sum_{i < j} d_{ij}}{n(n-1)/2} \quad \hat{\theta}_W = \frac{S}{\sum_{i=1}^{n-1} 1/i}$$

$$D = \frac{\hat{\theta}_T - \hat{\theta}_W}{\sqrt{\hat{V}(\hat{\theta}_T - \hat{\theta}_W)}}$$

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Test of Neutral Mutation Hypothesis

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TABLE 2—Continued

n	Confidence limit of D			
	90%	95%	99%	99.9%
150	-1.545 ~ 1.743	-1.769 ~ 2.089	-2.144 ~ 2.743	-2.477 ~ 3.443
175	-1.542 ~ 1.746	-1.765 ~ 2.095	-2.138 ~ 2.757	-2.470 ~ 3.470
200	-1.539 ~ 1.748	-1.760 ~ 2.100	-2.132 ~ 2.768	-2.462 ~ 3.492
250	-1.534 ~ 1.752	-1.754 ~ 2.107	-2.122 ~ 2.787	-2.449 ~ 3.529
300	-1.530 ~ 1.755	-1.748 ~ 2.114	-2.114 ~ 2.802	-2.439 ~ 3.558
350	-1.526 ~ 1.757	-1.744 ~ 2.119	-2.107 ~ 2.814	-2.430 ~ 3.581
400	-1.523 ~ 1.759	-1.740 ~ 2.123	-2.101 ~ 2.824	-2.422 ~ 3.600
450	-1.521 ~ 1.761	-1.737 ~ 2.127	-2.096 ~ 2.833	-2.415 ~ 3.617
500	-1.519 ~ 1.763	-1.734 ~ 2.130	-2.092 ~ 2.840	-2.409 ~ 3.632
600	-1.515 ~ 1.765	-1.728 ~ 2.135	-2.084 ~ 2.853	-2.398 ~ 3.657
800	-1.510 ~ 1.769	-1.721 ~ 2.143	-2.072 ~ 2.873	-2.382 ~ 3.694
1000	-1.505 ~ 1.772	-1.715 ~ 2.150	-2.062 ~ 2.887	-2.369 ~ 3.722

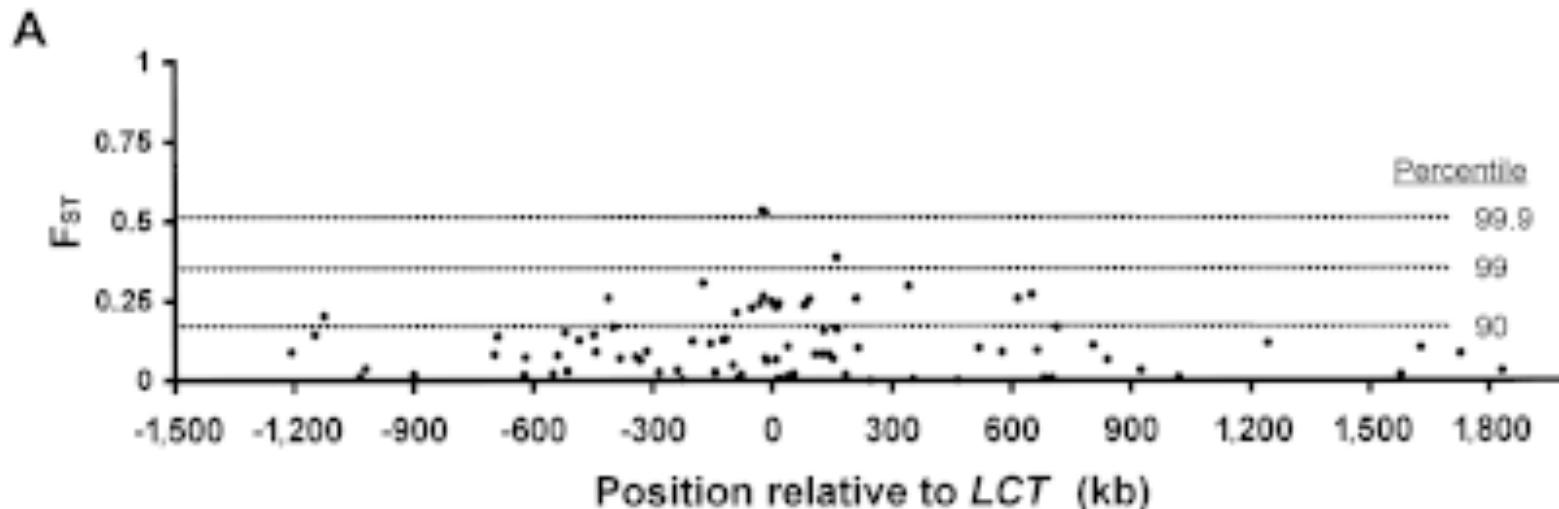
Population differences



- Different populations ~ different environments
- Different environments ~ distinct adaptive traits
- Selection acting in an environment on a locus in a local population but not all populations
- Population differentiation can be measured with F_{ST} (Wright's fixation index): compares the variance of allele frequencies *between* populations
 - Large F_{ST} values ~ strong differentiation between populations: directional, positive selection
 - Small F_{ST} values ~ populations are homogeneous: balancing selection

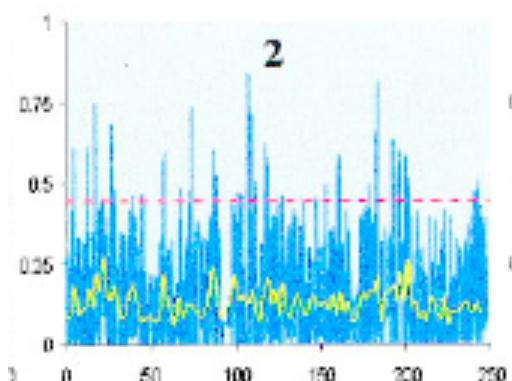
Genetic Signatures of Strong Recent Positive Selection at the Lactase Gene

Todd Bersaglieri,¹ Pardis C. Sabeti,³ Nick Patterson,³ Trisha Vanderploeg,¹ Steve F. Schaffner,³ Jared A. Drake,¹ Matthew Rhodes,^{1,*} David E. Reich,^{2,3} and Joel N. Hirschhorn^{1,2,3}



Interrogating a High-Density SNP Map for Signatures of Natural Selection

Joshua M. Akey,¹ Ge Zhang,¹ Kun Zhang,^{1,2} Li Jin,¹ and Mark D. Shriver^{3,4}



Length of haplotype



- Natural selection leaves footprints on genomes
- ~ Tajima's D: selective sweep affects whole haplotypes -> extension
- Extended haplotype homozygosity (EHH); long range haplotype(LRH); integrated haplotype score (iHS)

OPEN  ACCESS Freely available online

PLOS BIOLOGY

A Map of Recent Positive Selection in the Human Genome

Benjamin F. Voight[✉], Sridhar Kudaravalli[✉], Xiaoquan Wen, Jonathan K. Pritchard*

Length of haplotype: the composite iHS statistic

1/ measure EHH ~ the decay of identity as a function of distance of haplotypes that carry a specific ('core') allele at one end

EHH varies between 0 and 1, where haplotype homozygosity for the core SNP starts at 1 and decays to 0 with increasing distance from the core SNP

EHH is computed on haplotypes with the ancestral allele and with the derived allele and the area under the curve (EHH decay over distance) is kept ~ integrated EHH (iHH_A and iHH_D)

2/ $iHS = iHH_A/iHH_D$, where

$iHS=1$ if decay is similar between haplotypes carrying either alleles

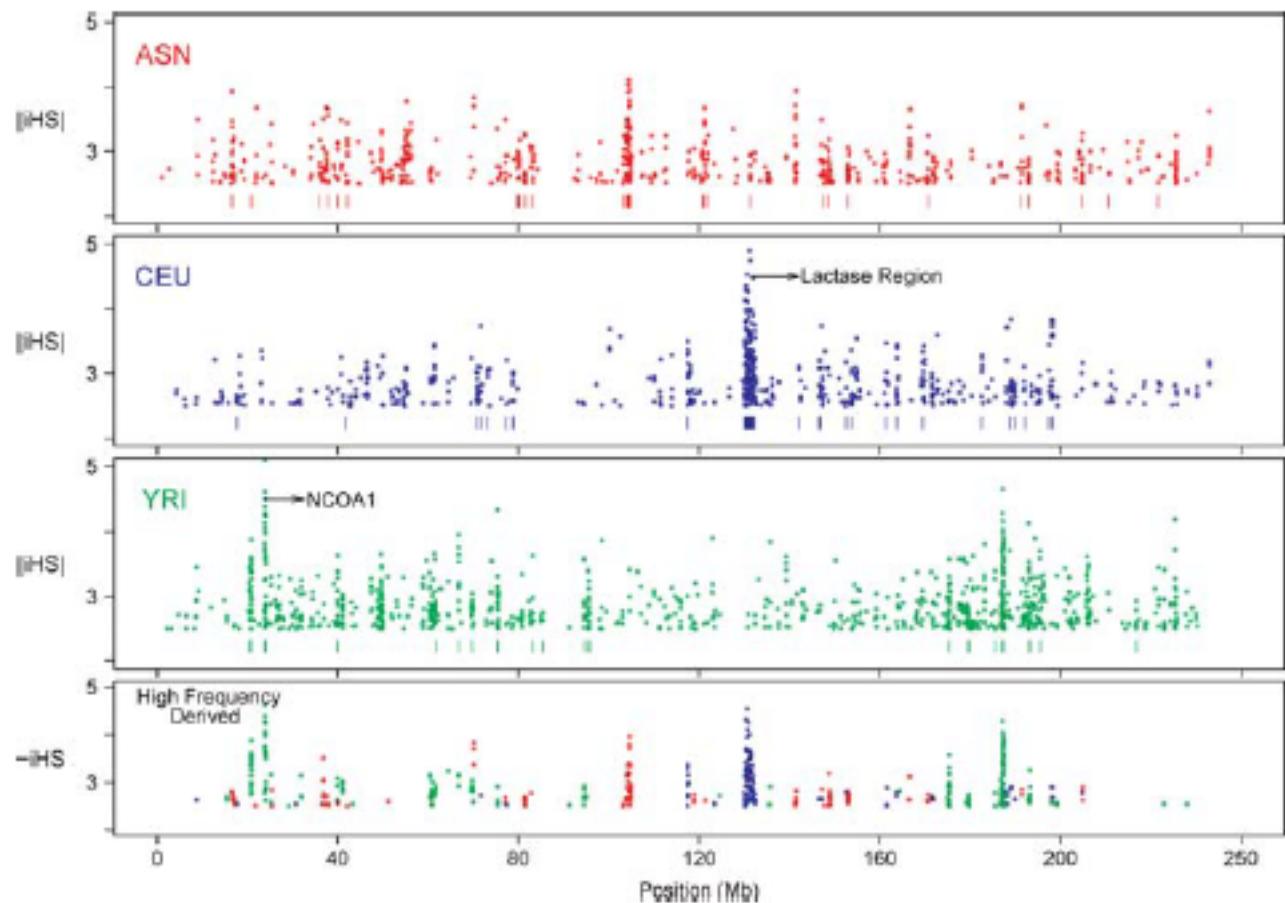
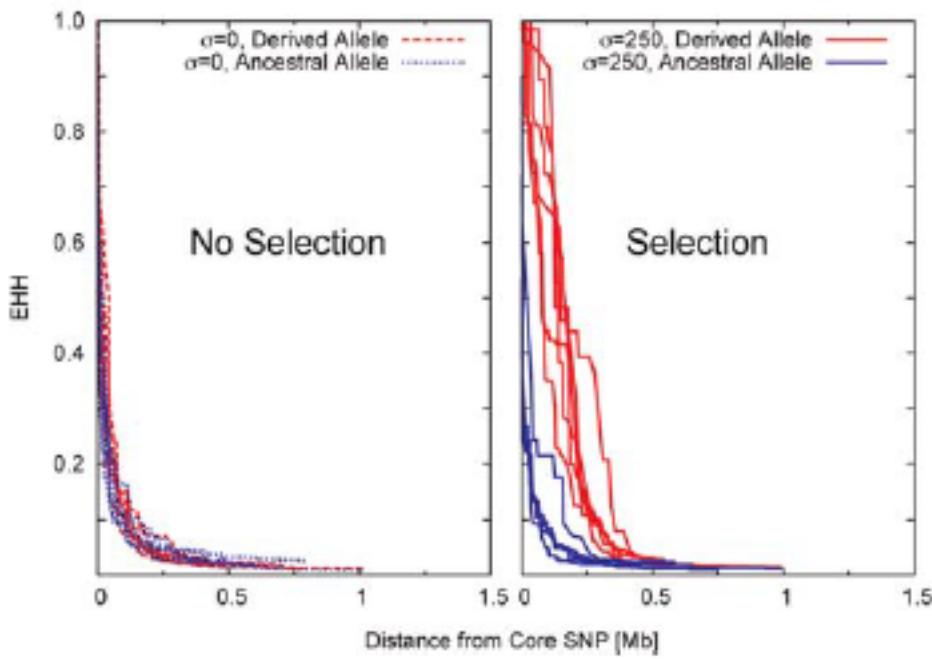
$iHS \ll 0$ if haplotypes carrying the derived allele are longer

$iHS \gg 0$ if haplotypes carrying the ancestral allele are longer

!! Sensitive to allele frequency: adjust/allele frequency and iHS mean and variance

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Many tests exist...

- PBS and XPEHH ~ population differences
- EHH ~ long range haplotypes
- Reviews:
 - Nielsen 2005 Ann Rev Genet
 - Vitti et al. 2013 Ann Rev Genet

Some examples

Population Genomics Reveal Recent Speciation and Rapid Evolutionary Adaptation in Polar Bears

Shiping Liu^{1,2,20}, Elime D. Lorenzen^{3,4,20}, Matteo Fumagalli^{3,20}, Bo Li^{1,20}, Kelley Harris⁵, Zijun Xiong¹, Long Zhou¹, Thorfinn Sand Korneliussen⁴, Mehmet Somel^{3,21}, Courtney Babbitt^{6,7,22}, Greg Wray^{5,7}, Jianwen Li¹, Weiming He^{1,2}, Zhuo Wang¹, Wenjing Fu¹, Xueyan Xiang^{1,2}, Claire C. Morgan⁹, Aoife Doherty¹⁰, Mary J. O'Connell⁹, James O. McInerney¹⁰, Erik W. Born¹¹, Lone Dalén¹², Rune Dietz¹³, Ludovic Orlando⁴, Christian Sonne¹³, Guojie Zhang^{1,14}, Rasmus Nielsen^{1,2,15,16,*}, Eske Willerslev^{4,*} and Jun Wang^{1,16,17,18,19,*}

Genome-wide detection and characterization of positive selection in human populations

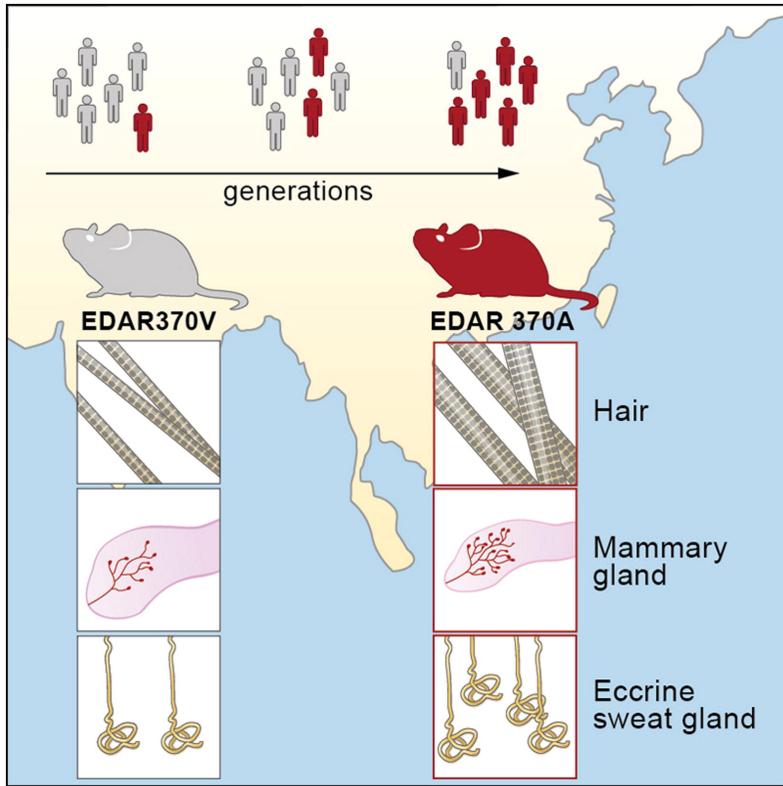
Pardis C. Sabeti^{1,*}, Patrick Varilly^{1,*}, Ben Fry¹, Jason Lohmueller¹, Elizabeth Hostetter¹, Chris Cotsapas^{1,2}, Xiaohui Xie¹, Elizabeth H. Byrne¹, Steven A. McCarroll^{1,2}, Rachelle Gaudet³, Stephen F. Schaffner¹, Eric S. Lander^{1,4,5,6}, and The International HapMap Consortium

HUMAN GENETICS

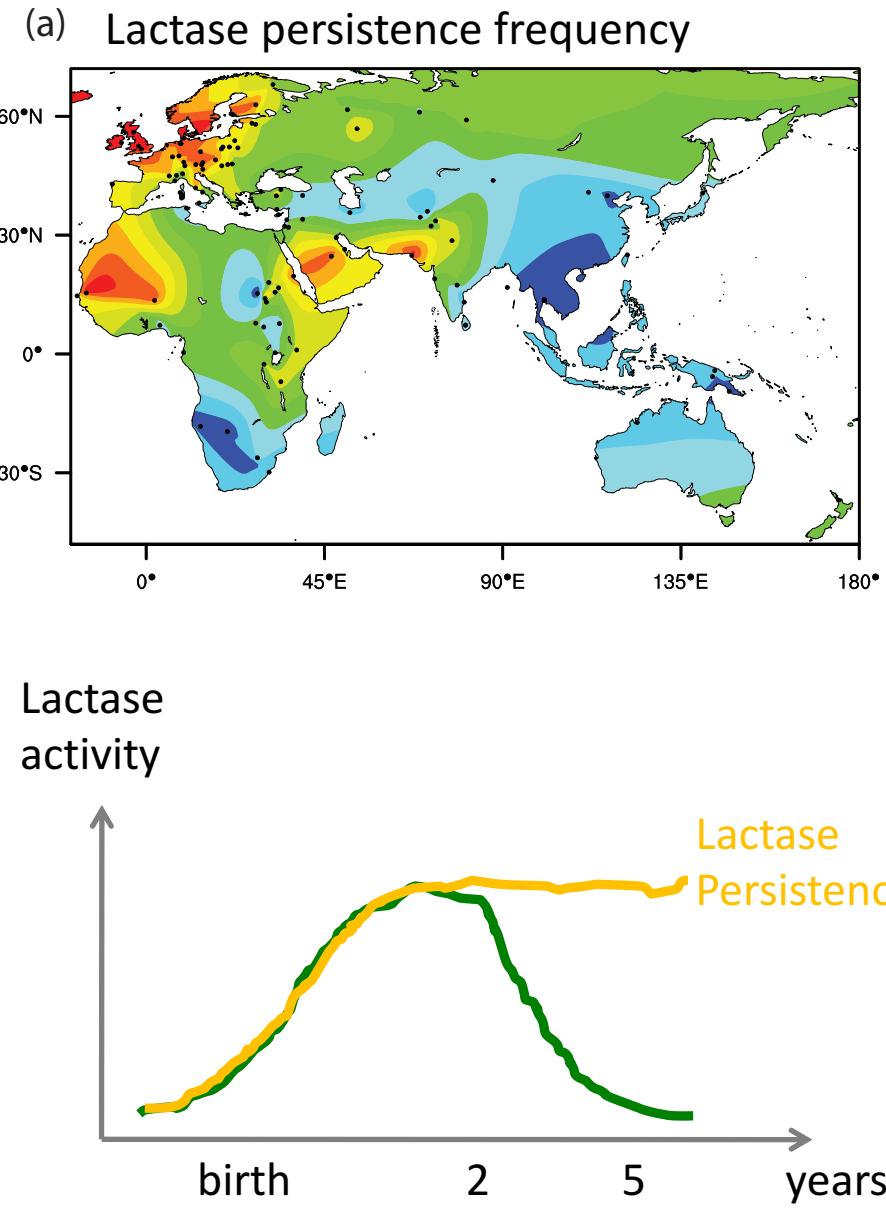
Greenlandic Inuit show genetic signatures of diet and climate adaptation

Matteo Fumagalli^{1,2,*}, Ida Moltke^{3,*}, Niels Grarup⁴, Fernando Racimo², Peter Bjerregaard^{5,6}, Marit E. Jørgensen^{5,7}, Thorfinn S. Korneliussen⁸, Pascale Gerbault^{1,9}, Line Skotte³, Allan Linneberg^{10,11,12}, Cramer Christensen¹³, Ivan Brandslund^{14,15}, Torben Jørgensen^{10,16,17}, Emilia Huerta-Sánchez¹⁸, Erik B. Schmidt^{17,19}, Oluf Pedersen⁴, Torben Hansen^{4,†}, Anders Albrechtsen^{3,†}, Rasmus Nielsen^{2,20}

Specific examples for the practical today



Kamberov et al. 2013 Cell



Gerbault et al. 2011 Phil Trans Roy Soc

Aims for the morning

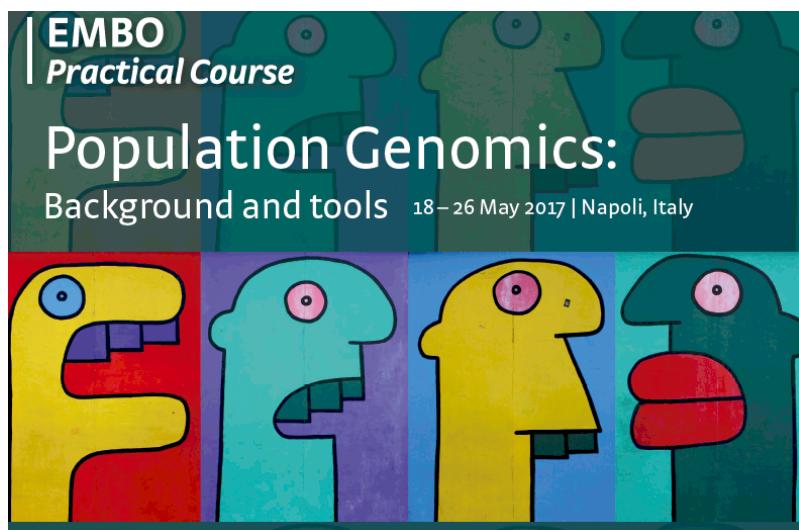
- THINK... together ;-)
- Series of commands used to generate the files from 1000 genomes data > what do they mean?
- Text files with statistics for EDAR~ SNP in Asians and LCT ~ SNP in Europeans > should be read/analysed in R: understand the commands and the statistic
- If you're fast: keep playing or have a break
- Any questions: PLEASE ASK :-)

With thanks to... YOU ☺

- * Matteo Fumagalli, Imperial College London
- * Garrett Hellenthal, University College London
- * Andrea Manica, University of Cambridge

Saki Raheem, Linda Percy, Caroline Smith, University of Westminster

Enza and Chiara



Information to find	Team 1	Team 2	Pascale
EDAR rs number			
EDAR chromosome location			
EDAR allele associated with hair thickness frequency in East Asians			
LCT allele associated with lactase persistence rs number			
LCT chromosome location			
LCT allele frequency in Europeans			
1000 genome assembly			
selscan data format			
Command lines...			