Genetics and Evolution

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BISC 577

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Disclaimers and Attributions

It is obviously impossible to cram everything to do with "Genetics and Evolution" into a lecture. I will not do justice to any topic I cover. Thus I will lightly touch upon a number of main themes, hoping to interest you to seek more information.

The lecture (and myself) had been heavily influenced by the work and teaching of Alkes Price, Graham Coop, and John Novembre.

What is Population Genetics?

Population genetics is the study of genetic variation, both within and between (human) populations.

It is the study of population genetic mechanisms (**mutations, assortative mating, migration, drift, recombination, and selection, etc.**) and how these forces shape the pattern of genetic variation.

Nothing in biology makes sense except in light of evolution. –T. Dobzhansky (1973)
Nothing in evolution makes sense except in light of population genetics. –M. Lynch (2005)

Are different human populations actually genetically different?

https://www.universiteitleiden.nl/en/research-dossiers/language-diversity

Slightly.

5-7% of worldwide human genetic variation is due to genetic differences between human populations.

The remaining 93-95% of human genetic variation is due to genetic variation **within** human populations (Rosenberg et al. 2002 Science)

Does "race" exist?

As Europeans explored and colonised the world [over the last few centuries], thinkers, philosophers and scientists from those countries attempted to apply taxonomic structures to the people that they encountered, and though these attempts were many and varied, they typically reflected sharp geographic boundaries, and obvious physical characteristics, such as pigmentation and basic morphology – that is to say, what people look like.

--Birney, Raff, Rutherford, and Scally. 2019

- http://ewanbirney.com/2019/10/race-genetics-and-pseudoscience-an-explainer.html

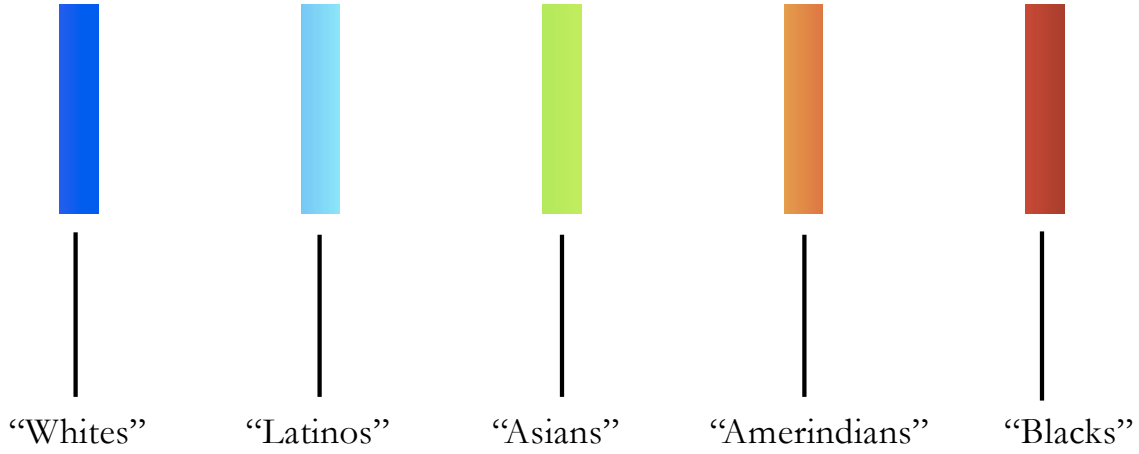
Does “race” exist? Not by genetics

Racial classifications are inadequate descriptors of the distribution of human genetic variation. (Tishkoff & Kidd, 2004 Nat. Genet.)

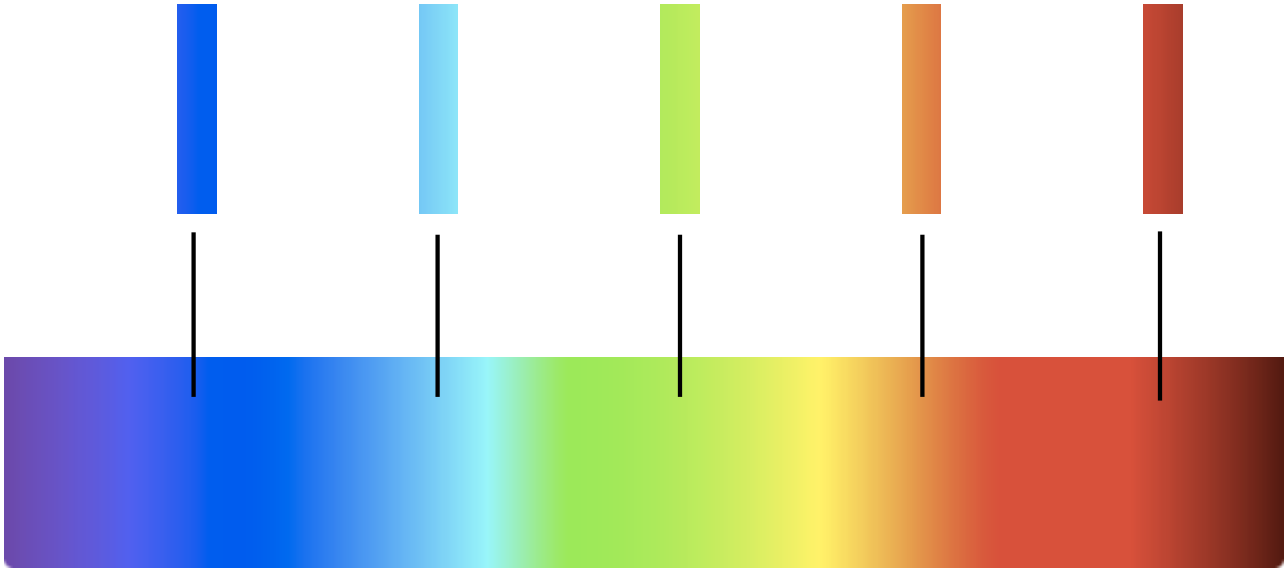
World-wide patterns of human genetic variation are best described using continuous clines instead of discrete clusters. (Serre & Paabo, 2004 Genome Res.)

If an alien, arriving on Earth with no knowledge of our social history, wished to categorise human ancestry purely on the basis of genetic data, they would find that any consistent scheme must include many distinct groups within Africa that are just as different from each other as Africans are to non-Africans. (Birney et al.)

Does "race" exist? Not by genetics

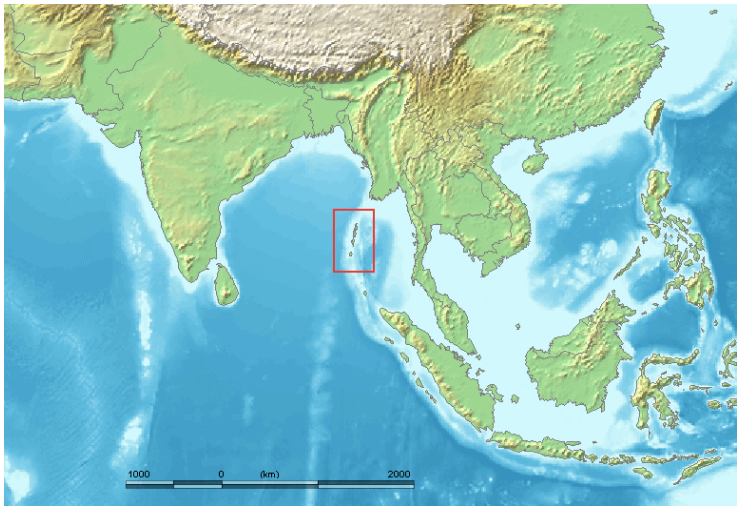


Does “race” exist? Not by genetics



What "race" are these individuals?

Onge population, one of the Andamanese indigenous people of the Andaman Islands



Of course, sometimes geneticists aren't helping…

Multiethnic Genome-Wide Association Study of Diabetic Retinopathy Using Liability Threshold Modeling of Duration of Diabetes and Glycemic Control

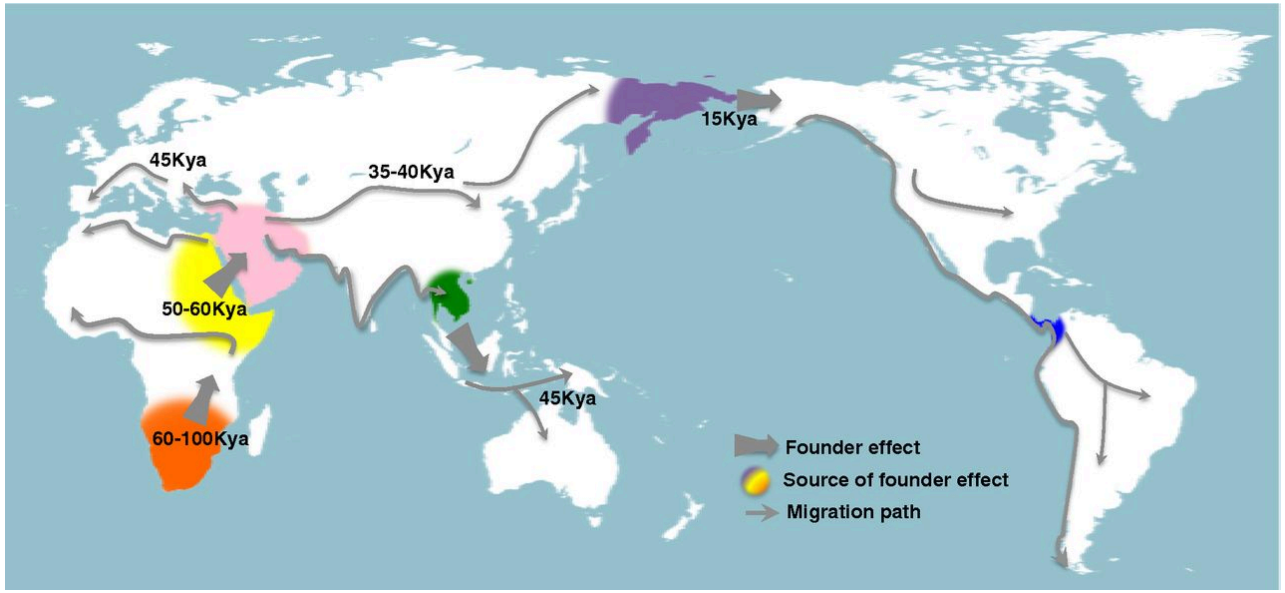
Diabetes 2019;68:441–456 | https://doi.org/10.2337/db18-0567

To identify genetic variants associated with diabetic retinopathy (DR), we performed a large multiethnic genome-wide association study. Discovery included eight European cohorts (n = 3,246) and seven African American cohorts (n = 2,611). We meta-analyzed across cohorts using inverse-variance weighting, with and without liability threshold modeling of glycemic control and duration of diabetes. Variants with a P value <1 × 10^{-5} were investigated in replication cohorts that included 18,545 European, 16,453 Asian, and 2,710 Hispanic subjects. After correction for multiple testing, the C allele of rs142293996 in an intron of nuclear VCP-like (*NVL*) was associated with DR in European discovery cohorts (P = 2.1 × 10^{-9}), but did not reach genome-wide significance after meta-analysis with replication cohorts. We applied the Disease Association Protein-Protein Link Evaluator (DAPPLE) to our discovery results to test for evidence of risk being spread across underlying molecular pathways. One protein–protein interaction network built from genes in regions associated with proliferative DR was found to have significant connectivity (P = 0.0009) and corroborated with gene set enrichment analyses. These findings suggest that genetic variation in *NVL*, as well as variation within a protein–protein interaction network that includes genes implicated in inflammation, may influence risk for DR.

Diabetic retinopathy (DR) is a leading cause of blindness (1). Established risk factors include longer duration of

Why study differences between human populations?

Learn about human migration patterns and ancient history



Henn et al. PNAS 2012

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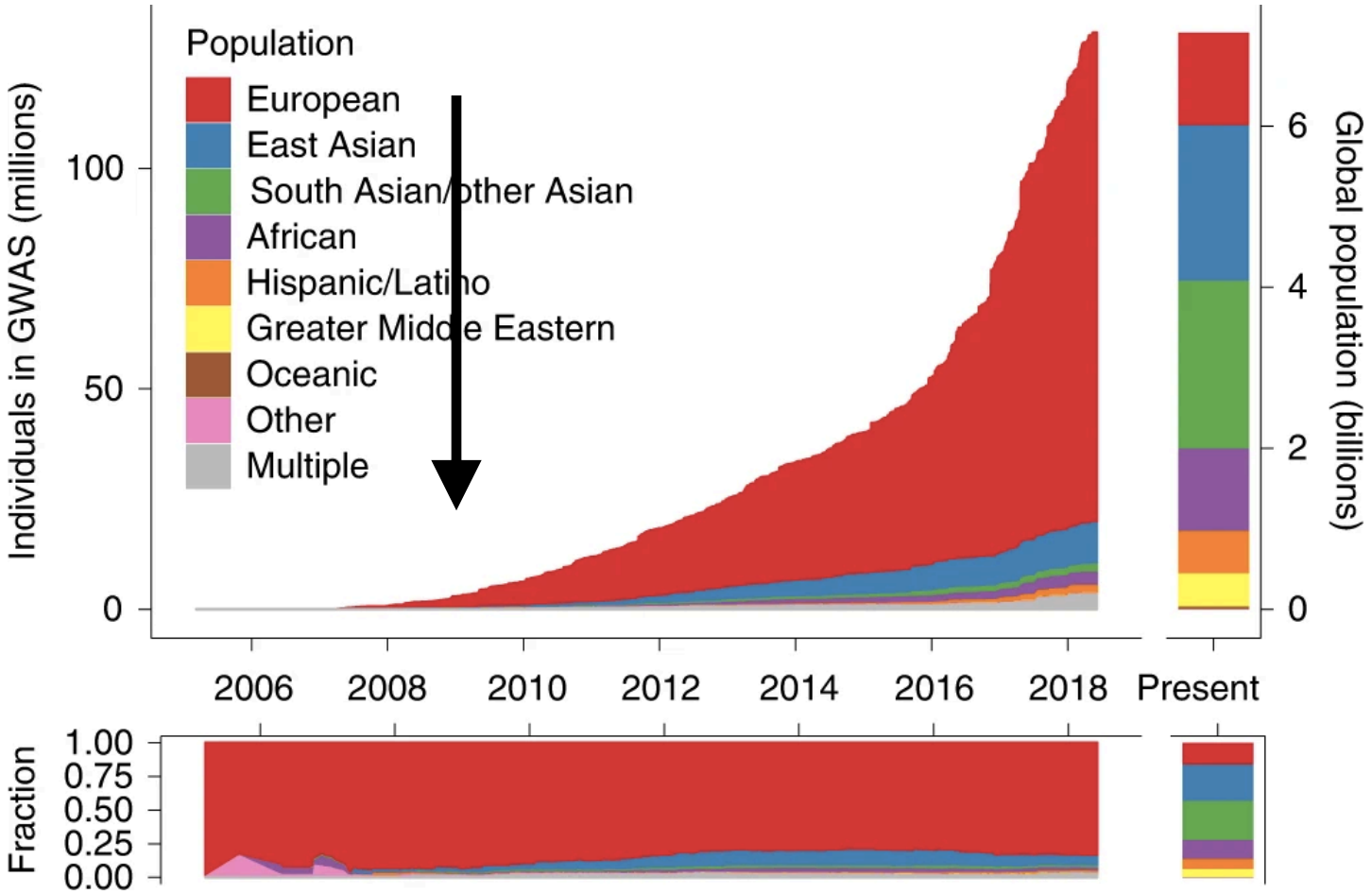
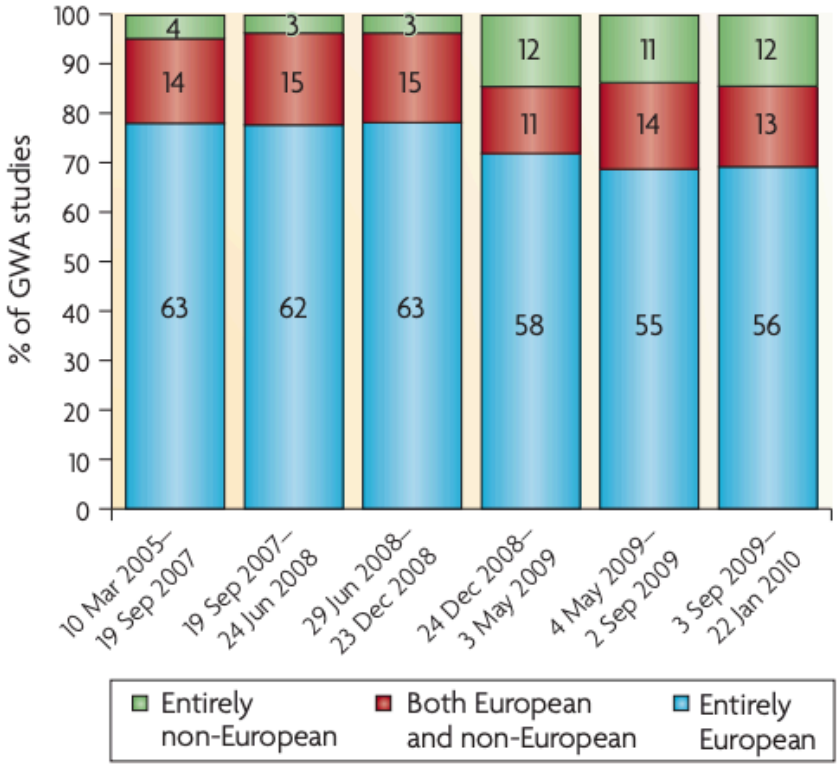
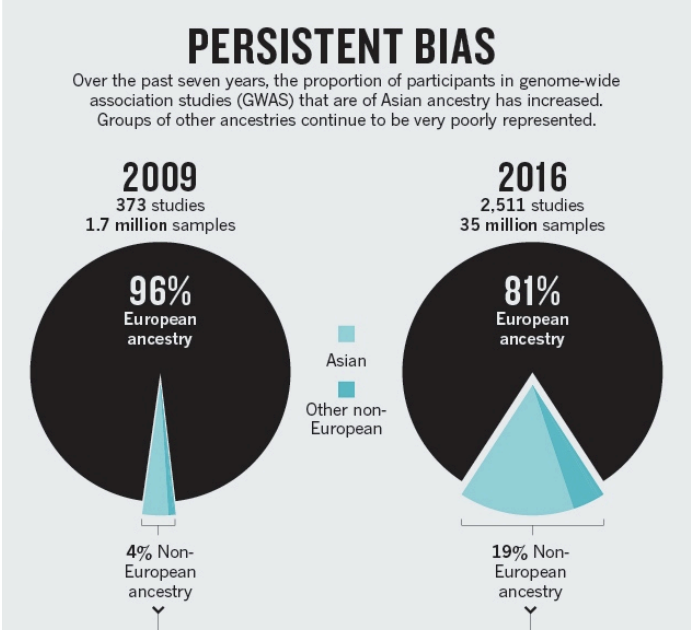
Improve our power to identify and localize disease genes



Martin et al. Nat. Genet. 2019





Rosenberg et al. Nat. Rev. Genet. 2010

Popejoy & Fullerton, Nature 2016

nature genetics

A thrifty variant in *CREBRF* strongly influences body mass index in Samoans

Ryan L Minster[1,13], Nicola L Hawley[2,13], Chi-Ting Su[1,12,13], Guangyun Sun[3,13], Erin E Kershaw[4], Hong Cheng[3], Olive D Buhule[5,12], Jerome Lin[1], Muagututi'a Sefuiva Reupena[6], Satupa'itea Viali[7], John Tuitele[8], Take Naseri[9], Zsolt Urban[1,14], Ranjan Deka[3,14], Daniel E Weeks[1,5,14] & Stephen T McGarvey[10,11,14]

LETTER

doi:10.1038/nature12828

Sequence variants in *SLC16A11* are a common risk factor for type 2 diabetes in Mexico

The SIGMA Type 2 Diabetes Consortium*

Why study differences between human populations?

Learn about human migration patterns and ancient history

Improve our power to identify and localize disease genes

- Differential patterns in linkage disequilibrium help with fine-mapping.
- Avoid false positives due to population stratification.
- Signals of natural selection at genes related to disease.

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Improve health disparity, promote personalized medicine

Lecture Outline

1. ~~Introduction and Motivation~~
2. Pattern of Genetic Variations
3. Population Genetic Forces that Impacts Genetic Variations
   - Demography
   - Natural Selection

What is genetic variation?

Genetic variation is the **difference in DNA** sequences between individuals. Variation occurs in **germ cells** (i.e. sperm and egg), and also in somatic cells.

Mutations and recombination are major sources of variation

There are many types of genetic variation:

- **Single Nucleotide Polymorphisms (SNP**) or Single Nucleotide Variants (SNV) …
- Structural Variants (SV): Insertions, Deletions, Inversions, Copy Number Variants (CNV), Duplications …
- Short Tandem Repeats (STR)
- Large scale chromosomal rearrangements …

What is a Single Nucleotide Polymorphism (SNP)?

It is a letter of the genetic code at a particular genomic position that differs in different individuals (e.g. chromosome 1, base pair 50,055,936, G/T).

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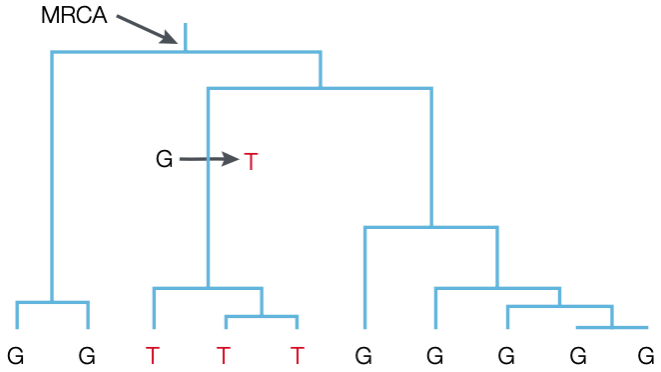
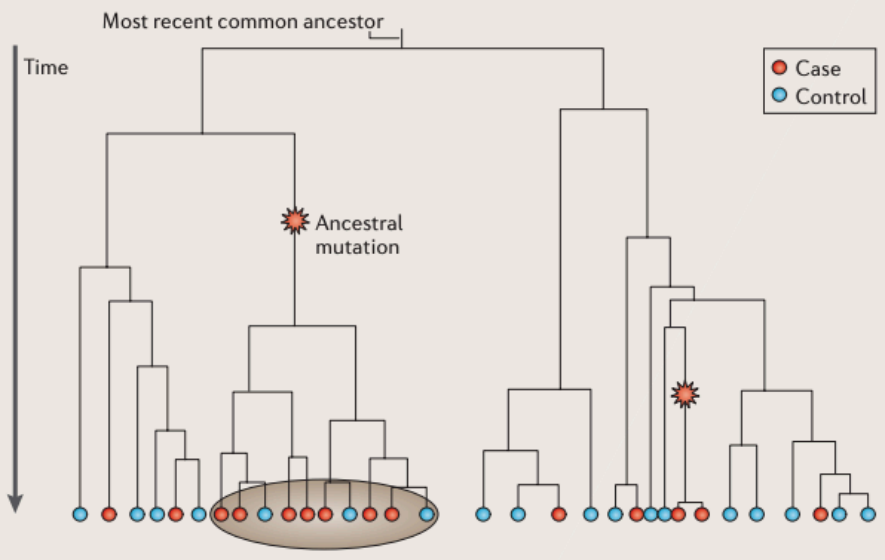
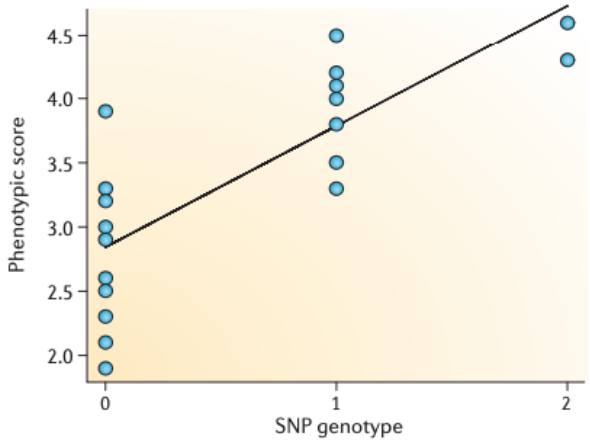
Each SNP is (typically assumed) to correspond to a single mutation event in history, e.g. G mutated to T in a single ancestor. Then G = **ancestral** allele, T = **derived** allele.



Rosenberg & Nordborg, Nat. Rev. Genet. 2002

Evolutionary Rationale for GWAS

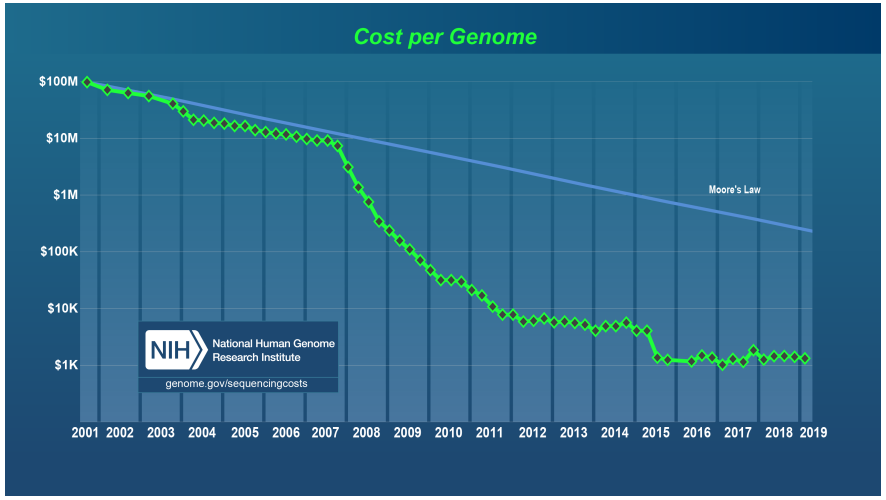




Balding, Nat. Rev. Genet. 2006

How do we ascertain genetic variation?

Sequencing (whole genome or whole exome), but until this day it is still not feasible at large scale.



Moore's Law is the empirical relationship that number of transistors in a dense integrated circuit doubles about every two years. It's a projection of increase in computer power and decrease in relative cost.

How do we ascertain genetic variation?

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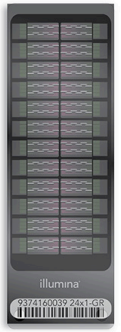
Historically (and still now), we relied on genotyping microarrays to genotype specific locations in the human genome known to harbor SNP variation.

Affymetrix



Illumina

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Sequencing (whole genome or whole exome), but until this day it is still not feasible at large scale.

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Thus, we relied on large database of SNP variation.

Affymetrix

Illumina

The International HapMap Consortium

Phase 1: Launched in 2002, completed in 2005, targeted > 1M SNPs in the genome for genotyping in 4 populations (269 samples).

Some SNP discovery efforts (shot-gun sequencing in limited samples), combined with dbSNP and whatever information available at the time. Then designed SNP assays in 5kb bins at a time across the genome. Limited use of arrays (40K and 120K)

Population Label	Population Name	Sample Size
CEU	Utah residents with Northern and Western European ancestry from CEPH collection	90
CHB	Han Chinese in Beijing, China	45
JPT	Japanese in Tokyo, Japan	44
YRI	Yoruba in Ibadan, Nigeria	90

HapMap Project Summary

Project	HapMap		
Phase	1	2	3
Year Complete	2005	2007	2010
Sample Size	269	270	1184
Populations	4	4	11
# variants	1 M	3.1 M	1.6 M + CNVs

Beyond HapMap, what does the world still need?

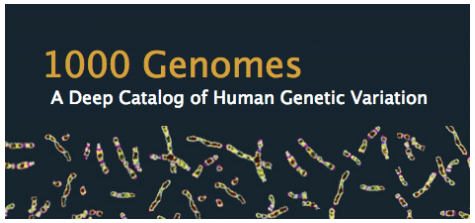
Larger sample sizes

More complete representation of global diversity!

Better discovery and characterization of structural and copy number variation (still an area being developed)

More complete description of the frequency spectrum! Particularly the **low-frequency and rare variants** (minor allele frequency < 0.05)

The 1000 Genomes Project

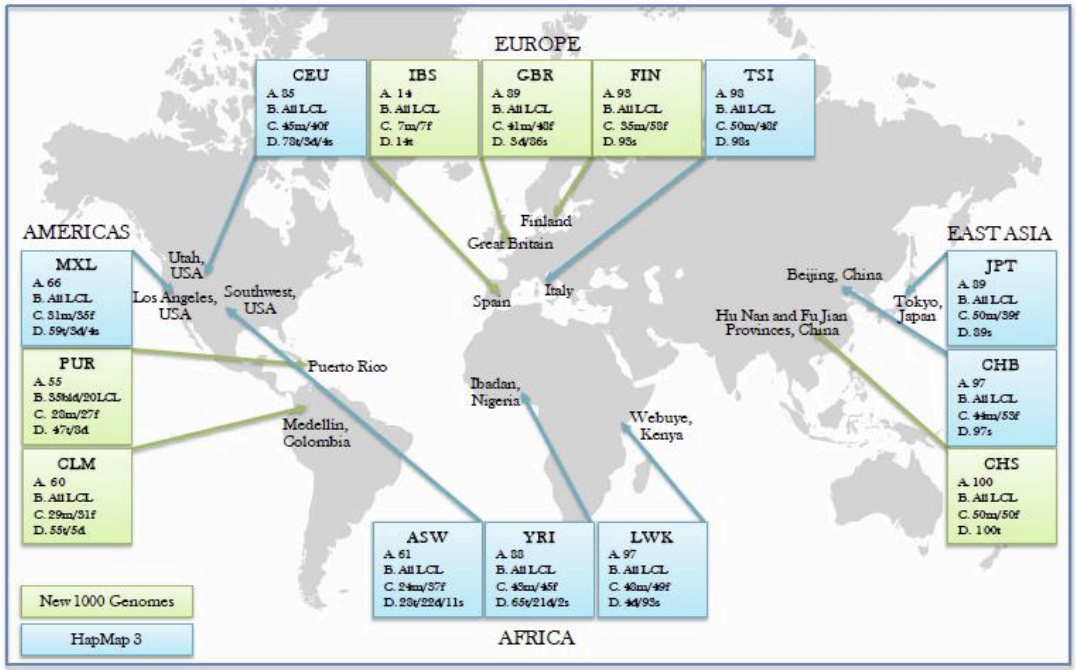


Phase 1: completed 2012

Sequenced the entire genome of 1,092 individuals from 4 super-populations (EUR, EAS, AFR, AMR; 14 populations total).

Next-gen sequencing technology (~4x; Illumina, 454, SOLiD…)

38M SNPs, 1.4M indels, estimate captured 98% of accessible SNPs with MAF > 0.01



The 1000 Genomes Project Consortium, Nature 2012

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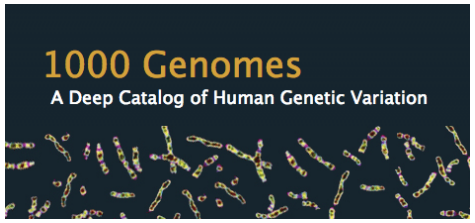


Phase 3: completed 2015

2,504 individuals from 5 super-populations (EUR, EAS, AFR, AMR, SAS; 26 populations total).

NGS Illumina only, ~7x

85M SNPs, 3.6M indels. 64M have MAF < 0.5%.

Estimate captured 99% of accessible SNPs with MAF > 0.01.

The 1000 Genomes Project Consortium, Nature 2015

The future?

NHLBI Trans-Omics for Precision Medicine

TOPMed: began in 2014. ~149K individuals from >80 disease cohorts.

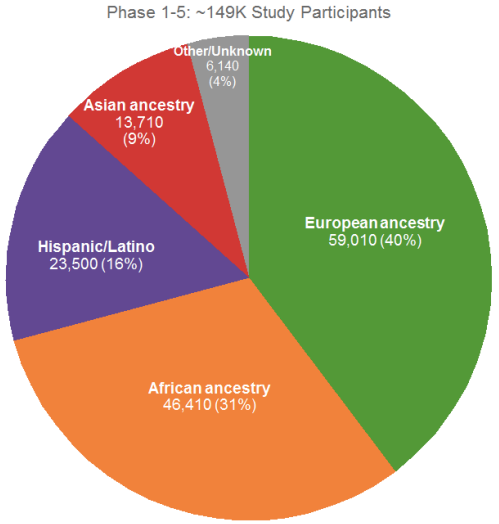
Median depth ~30X whole genome.

Freeze 5 on 53.5K individuals now "available"

- Taliun et al., bioRxiv 2019
- > 400M SNPs and indels, 97% are < 1% MAF, 46% singletons

Freeze 8 on > 140K individuals released mid-2020

- > 800M SNPs, > 66M indels …



In ~two decades since HGP…

Project	HapMap		
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Year Complete	2005	2007	2010
Sample Size	269	270	1184
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* Phase 2 with ~1700 samples sequenced was largely used for methods development

Exome Aggregation Consortium (ExAC), 2016:

60,706 individual exomes (7.1M SNPs, 0.3M indels)

Genome Aggregation Database (gnomAD), 2017-2019:

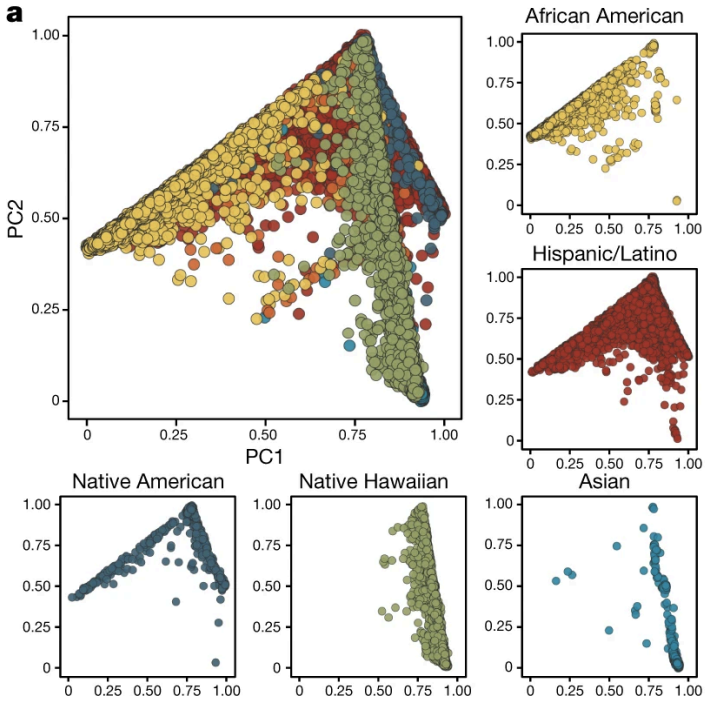
125,748 exomes (16M SNPs, 1.2M indels), 71,702 genomes (602M SNPs, 105M indels)

Also missing, all the major biobanks (UKB, 500K individuals that will be all WGS; BBJ > 160K individuals; etc.)

Side note about "populations"…

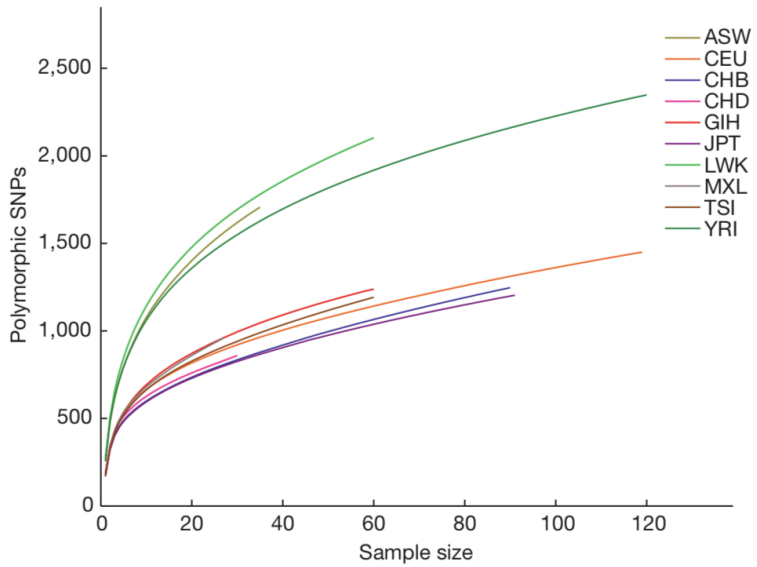
How many populations did TOPMed sequence?

- Sample of 'convenience'
- Disease cohorts in the United States
- But what is a population anyways?



What did we learn from these large databases of genetic variation?

African populations have more SNPs (per Mb)



International HapMap3 Consortium, Nature 2010

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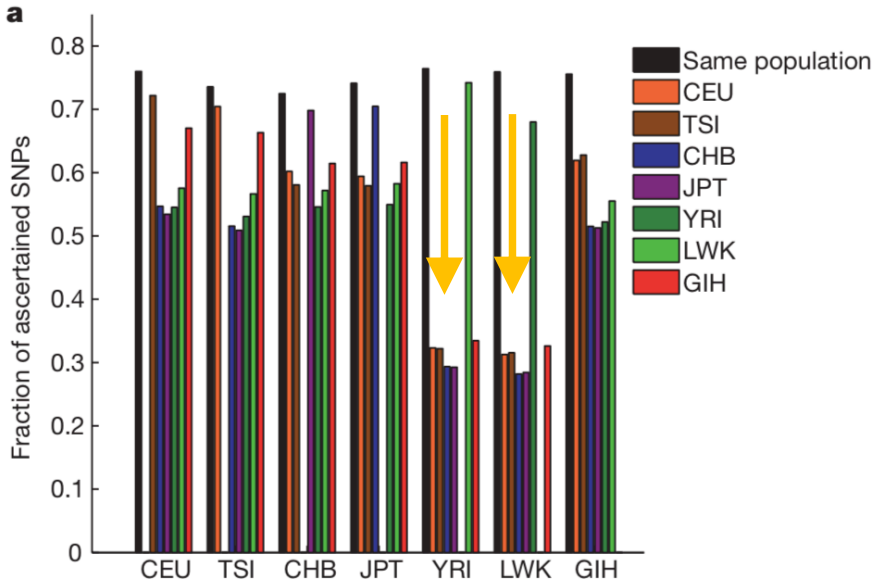
SNPs in non-Africans tend to be a subset of SNPs in Africans

Are SNPs ascertained in 30 individuals from x-axis population polymorphic in another 30 individuals from color-coded population?



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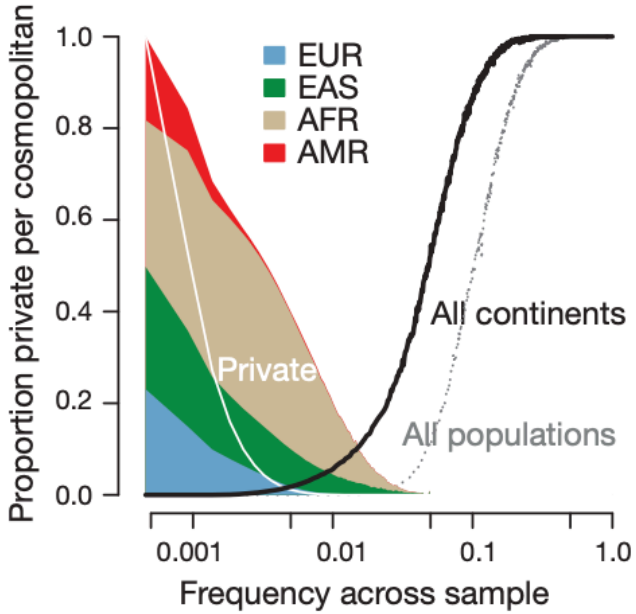
Common variants are shared across populations, but rare variants are often population-specific



The 1000 Genomes Project Consortium, Nature 2012

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The **block-like structure** of the genome

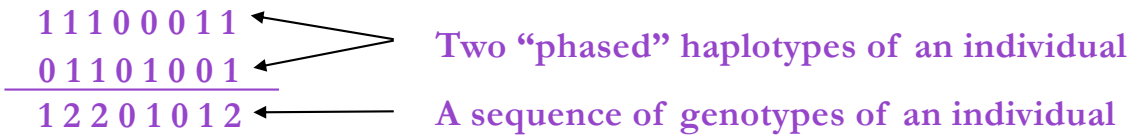
Some definitions first, just so we're clear

Haplotype: description of SNP alleles on a chromosome

- A vector of 0's and 1's, if e.g. 0 denote the ancestral allele, 1 denote the derived allele

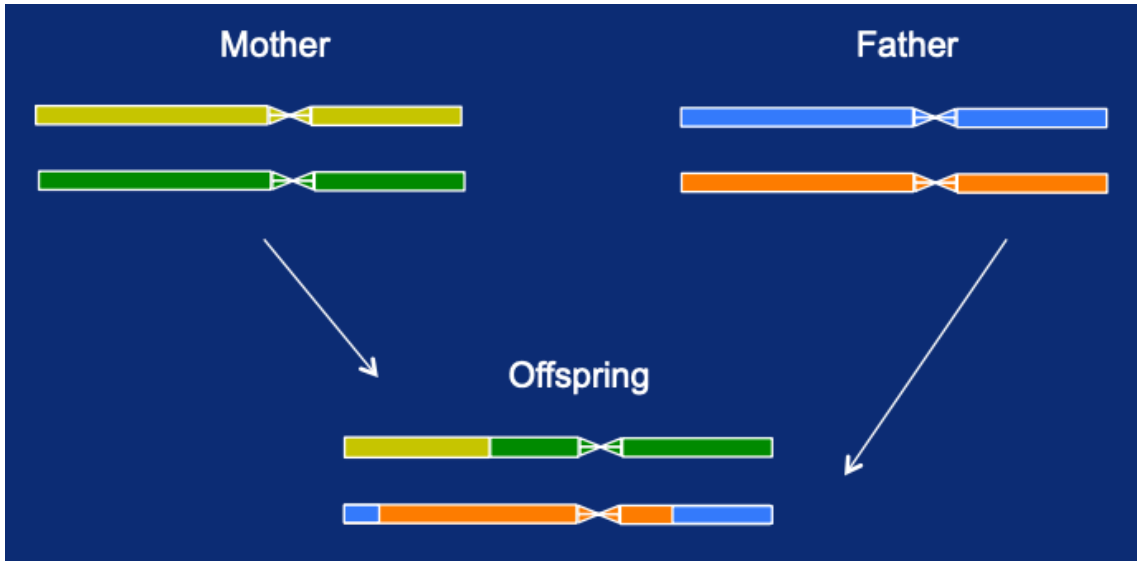
Genotype: description of alleles on both chromosomes in a person

- A vector of 0, 1, and 2's



Biospecimen containing DNA molecules is a mixture of the two copies of your haploid genome, so genotyping (and usually sequencing) tells you only the genotype. The phase of the haplotype can be statistically computed, using programs like EAGLE, SHAPEIT, BEAGLE …

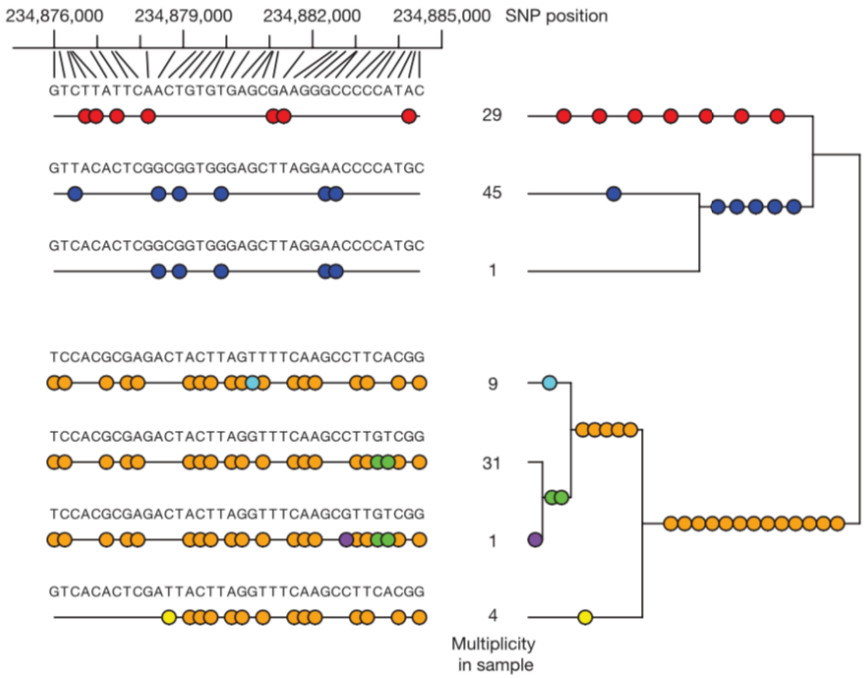
Your genome is inherited in blocks due to recombination being relatively rare



Recombination is uneven across the genome, occurs often in hotspots.

At a e.g. low recombination region of the genome, the entire chunk tend to be inherited together. Thus mutations arising on that chunk over time will be more associated with each other than variation outside of the chunk.

Block-like structure of the genome



Empirical region on chr2 with 36 SNPs. In theory, that should give rise to 2^36 different haplotypes. In practice, only 7 were observed (in *this* sample)

The non-random association between two SNPs as a result of this block-like structure, is known as **linkage disequilibrium (LD)**.

HapMap Consortium, Nature 2005

How is LD measured?

Consider two SNPs with frequencies p_A and p_B of alleles A and B, with phased data

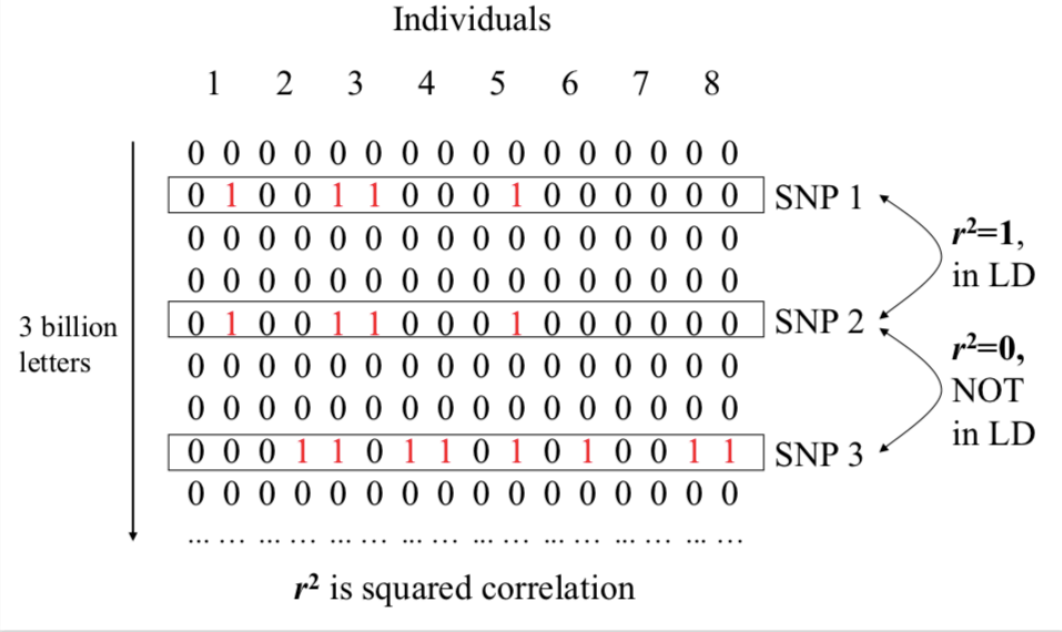
Main basis is deviation $D = p_{AB} - p_A p_B$, but typically we use r^2 or D'

r^2 is the correlation coefficient of 1/0 indicator variable indicating the presence of A and B

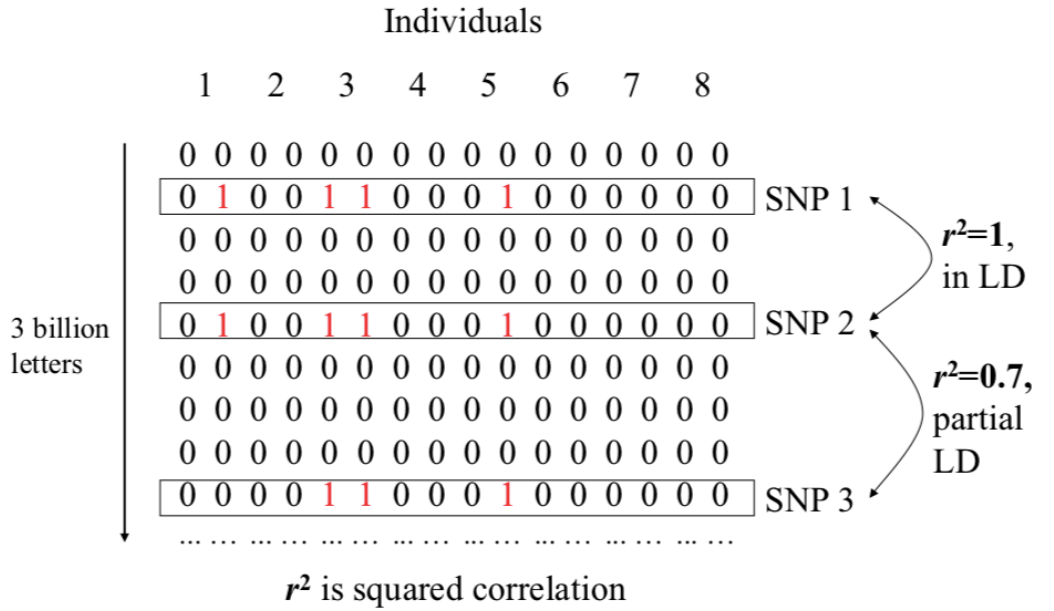
D' has the convenient property that when D' = 1, it means at least one of the four possible haplotypes is absent.

Slatkin, Nat. Rev. Genet. 2008

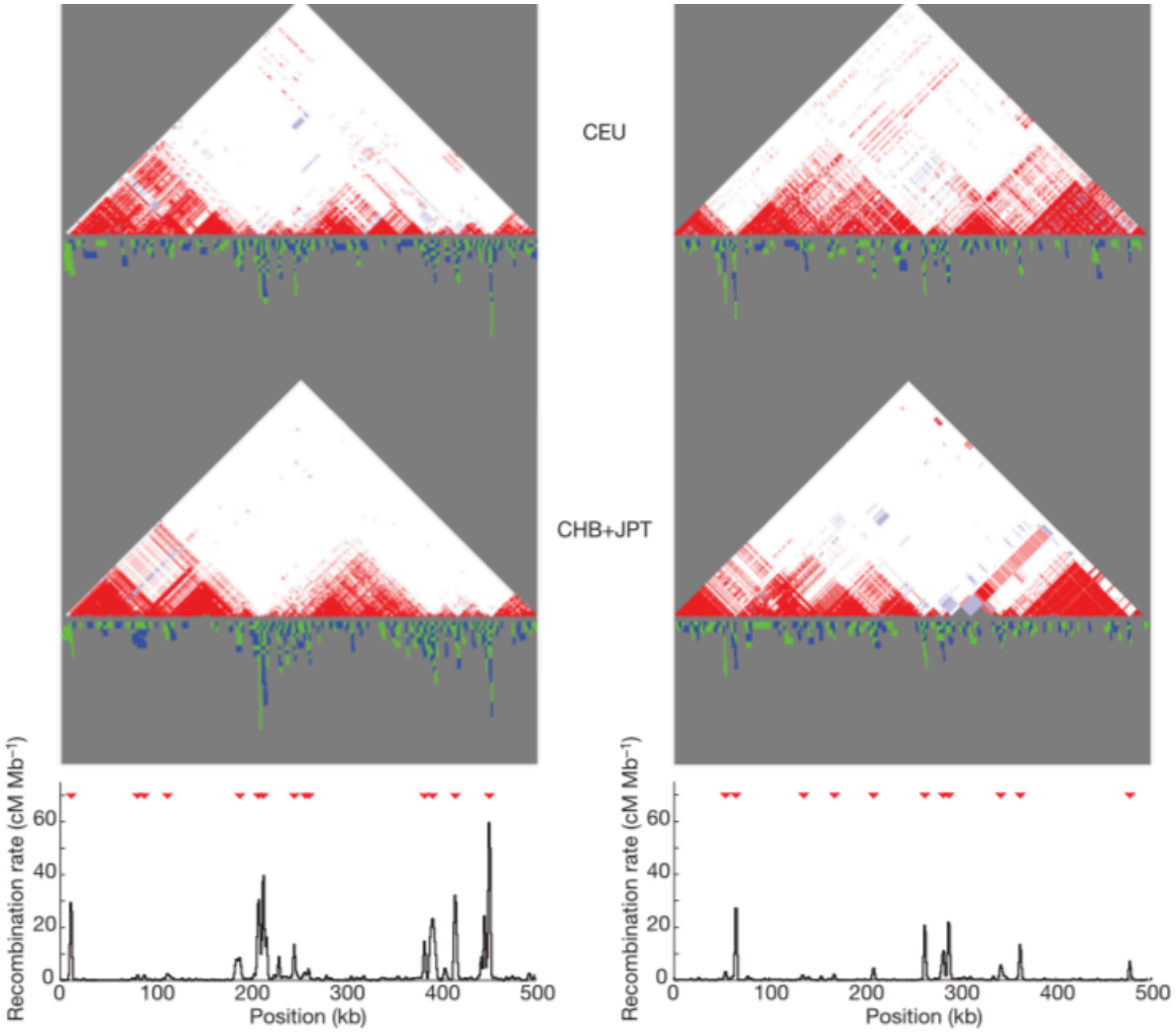
LD example


Individuals
1 2 3 4 5 6 7 8
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 1 0 0 1 1 0 0 0 1 0 0 0 0 0 0
SNP 1
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 1 0 0 1 1 0 0 0 1 0 0 0 0 0 0
SNP 2
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 1 1 0 1 1 0 1 0 1 0 0 1 1
SNP 3
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
3 billion letters
r²=1, in LD
r²=0, NOT in LD
r² is squared correlation

LD example


Individuals
1 2 3 4 5 6 7 8
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 1 0 0 1 1 0 0 0 1 0 0 0 0 0 0
SNP 1
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 1 0 0 1 1 0 0 0 1 0 0 0 0 0 0
SNP 2
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 1 1 0 0 0 1 0 0 0 0 0 0
SNP 3
3 billion letters
r^2=1, in LD
r^2=0.7, partial LD
r^2 is squared correlation

Haplotype blocks



HapMap Consortium, Nature 2005

Lecture Outline

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Now that we know about genetic variations…

Genetic variation is the **difference in DNA** sequences between individuals.

- Mutations contribute to new variations (SNPs if a point mutation)
- Recombination contribute to haplotype diversities (and can be potentially mutagenic, see Halldorsson et al. Science 2019)

The block-like structure enabled Genome-Wide Association Studies (GWAS), because you don't need to genotype and test the *actual* causal allele, but just genotype enough variation in the genome to capture one that is in LD with the causal allele.

What could have shaped the pattern of variation such that they differ between populations, potentially contribute to differential disease risks between them?

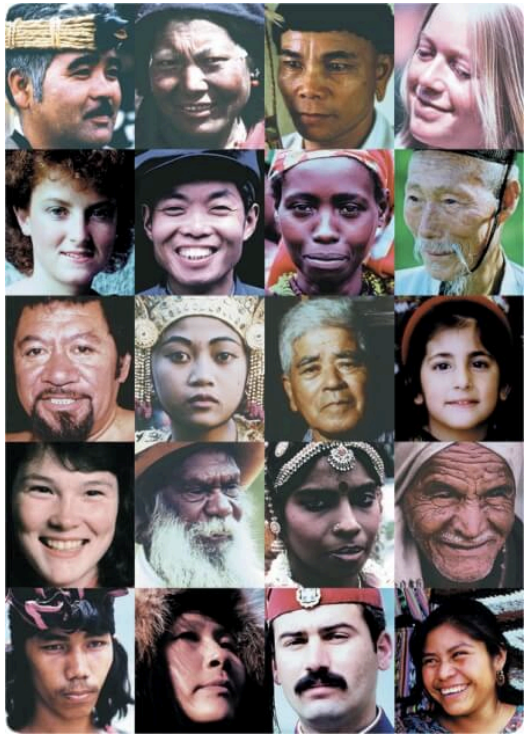
Population Genetic forces that shaped genetic variation

Demographic history

- Population structure
- Bottleneck
- Admixture

Natural Selection

Remember… genetic differences between populations are small, but do exist



93-95% of human genetic variation is due to variation **within** human populations (Rosenberg et al., Science 2002)

The predicted proportion of observed heterozygosity at a given genetic locus, **assuming human populations are randomly mating**, result in *only* an average error of 5-15% (Novembre & Peter, Curr Opin Genet Dev, 2016)

So, there is fine-scale structure in human populations. A small effect, but existent.

Population Structure

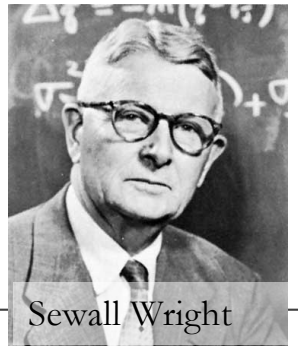
Population structure or **population subdivision** refers to genetic differences between (typically discrete) populations due to geographic ancestry

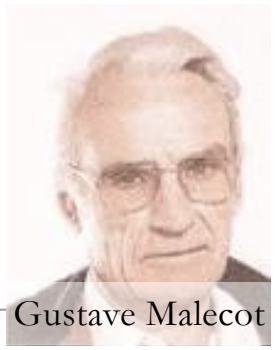
This is due to assortative mating. In other words, mating takes place within sub-groups of the whole population

A common model that could lead to population structure in humans is the **Isolation by Distance** model (Wright 1943; Malecot 1948)

Though the effect of population structure is relatively small, it can significantly confound genome-wide association studies of human phenotypes

Isolation-by-distance


Sewall Wright


Gustave Malecot

Isolation-by-distance is a simple consequence of limited dispersal across space. If pairs of populations are close to each other, they will be more genetically similar to each other than populations farther away from each other.

This is not because there is any selective need for genetic similarities, just because individual critters, or their seeds, or pollen, or larvae, etc. are less likely to travel longer distances.

But do note that other models exist, like Kimura's stepping stone model.

https://www.molecularecologist.com/2012/09/isolating-isolation-by-distance/

How to detect/visualize population structure?

"Discrete" population clusters

- Model-based clustering (STRUCTURE, FRAPPE, ADMIXTURE, TeraStructure, etc.)

"Continuous" population structure

- Principal Components Analysis (PCA)

Model-based clustering

Example: POP1 and POP2 with known allele frequencies

	SNP1	SNP2	SNP3	SNP4	…	
POP1	0.25	0.57	0.29	0.38	…	(allele frequencies)
POP2	0.40	0.32	0.84	0.22	…	(allele frequencies)
Ind X	2	0	1	1	…	(SNP genotypes)

Does individual X belong to POP1 or POP2?

P(DATA | X in POP1) is proportional to:
$(0.25)^2(0.75)^0(0.57)^0(0.43)^2(0.29)^1(0.71)^1(0.38)^1(0.62)^1 = 0.0006$
P(DATA | X in POP2) is proportional to:
$(0.40)^2(0.60)^0(0.32)^0(0.68)^2(0.84)^1(0.16)^1(0.22)^1(0.78)^1 =$ **0.0017**

Model-based clustering

Example: POP1 and POP2 with known allele frequencies

	SNP1	SNP2	SNP3	SNP4	…	
POP1	0.25	0.57	0.29	0.38	…	(allele frequencies)
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Ind X	2	0	1	1	…	(SNP genotypes)

If individual X has ancestry α from POP1 and (1- α) from POP2, then what is the most likely value of α?

P(DATA | α) is proportional to:

$$[0.25\alpha+0.40(1-\alpha)]^2[0.75\alpha+0.60(1-\alpha)]^0[0.57\alpha+0.32(1-\alpha)]^0[0.43\alpha+0.68(1-\alpha)]^2$$
$$[0.29\alpha+0.84(1-\alpha)]^1[0.71\alpha+0.16(1-\alpha)]^1[0.38\alpha+0.22(1-\alpha)]^1[0.62\alpha+0.78(1-\alpha)]^1$$

} max value 0.0020 attained at $\boldsymbol{\alpha = 0.22}$

Model-based clustering

These ideas can be generalized to M SNPs, N populations, with known allele frequencies p_{mn} for SNP m in population n, observed genotype count g_m for SNP m in individual X. Then one can assign the population $n = 1$ to N that individual belongs to, or assign the most likely fractional membership α to each population n.

Model-based clustering

This can be further generalized to many individuals X_i, with unknown allele frequency p_{mn} for SNP m in population n

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Then you model the joint likelihood:

P(DATA | $X_i \sim \alpha_{i1}, \ldots, \alpha_{iN}$ for each i; p_{mn}) is proportional to

$$\prod_{i=1}^{I} \prod_{m=1}^{M} \left(\sum_{n=1}^{N} \alpha_{in} p_{mn}\right)^{g_{im}} \left(\sum_{n=1}^{N} \alpha_{in}(1 - p_{mn})\right)^{2-g_{im}}$$

Then find values of α_{in}, p_{mn} which maximize this likelihood.

Model-based clustering

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Then find values of α_{in}, p_{mn} which maximize this likelihood.

The different approaches to maximize this likelihood is adopted by different program (EM, MCMC, variational Bayes approximations, etc.)

Model-based clustering

STRUCTURE (Pritchard et al. Genetics 2000)

FRAPPE (Tang et al. Genet. Epi. 2005)

ADMIXTURE (Alexander et al. Genome Res. 2009)

TeraStructure (Gopalanan et al. Nat. Genet. 2016)

…

Model-based clustering in action

Human Genome Diversity Panel data

- 1,056 individuals, 52 world populations
- 377 STR (multi-allelic)

Model-based clustering in action

Human Genome Diversity Panel data

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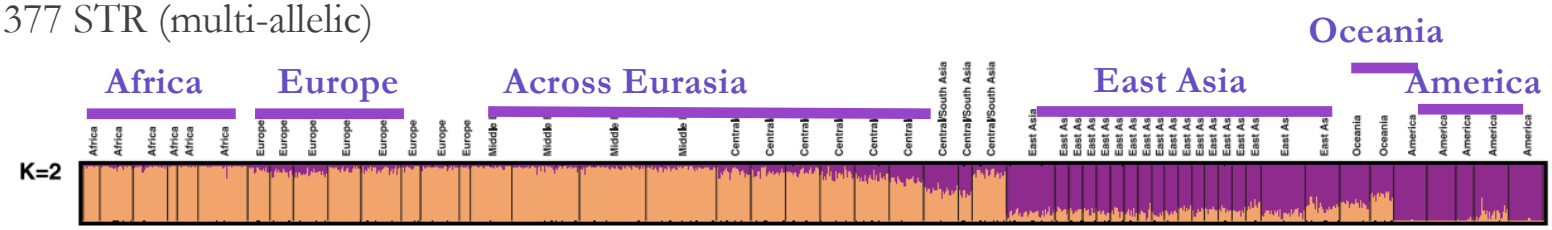
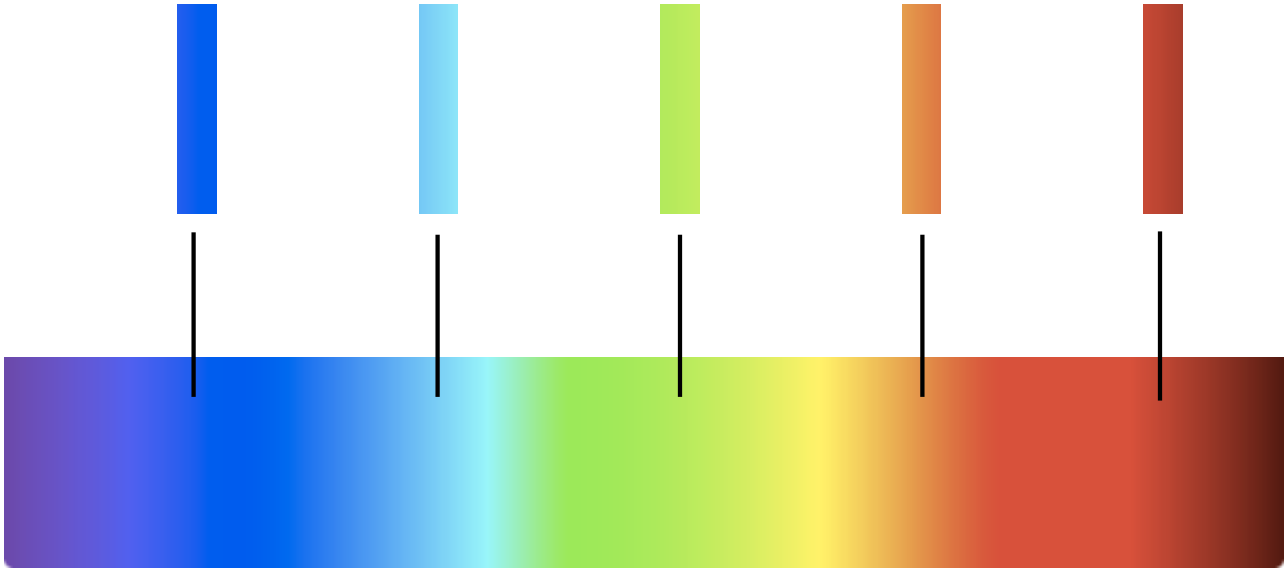
- 377 STR (multi-allelic)



Rosenberg et al. Science 2002

Does “race” exist? Not by genetics

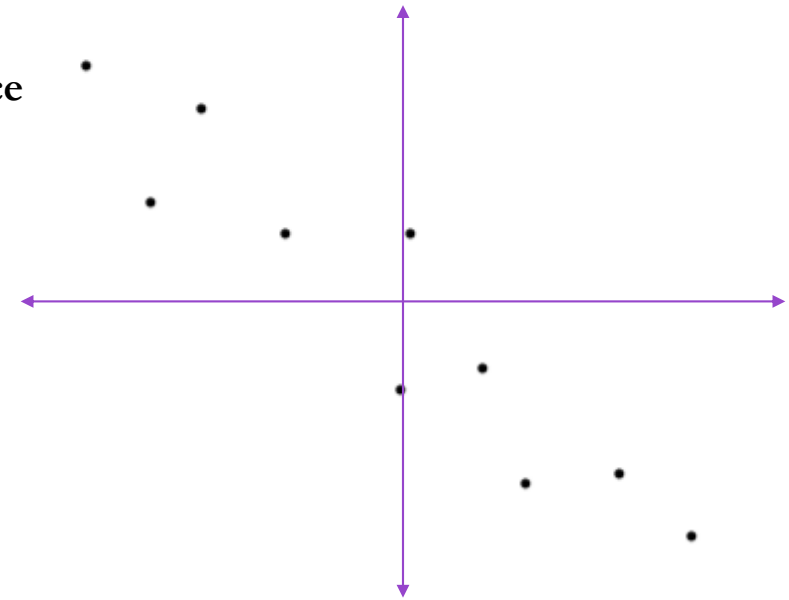


Principal Components Analysis

Principal Components Analysis, or **PCA**, is a dimension reduction technique that converts high dimensional data (such as human SNP data) into a set of linearly uncorrelated variables (principal components, or PCs). The transformation is done in such a way that the first principal component has the largest possible variance explained.

PCA, an intuition

10 points in 2-dimensional space



PCA, an intuition

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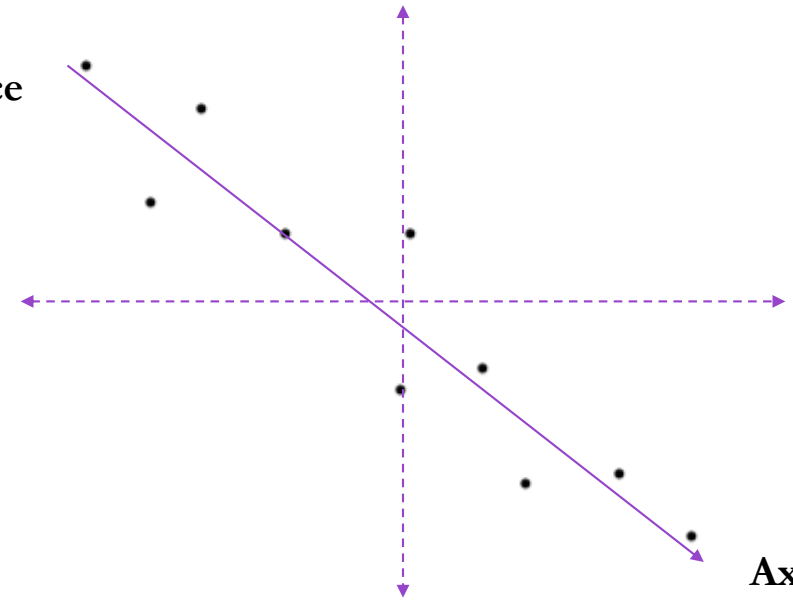
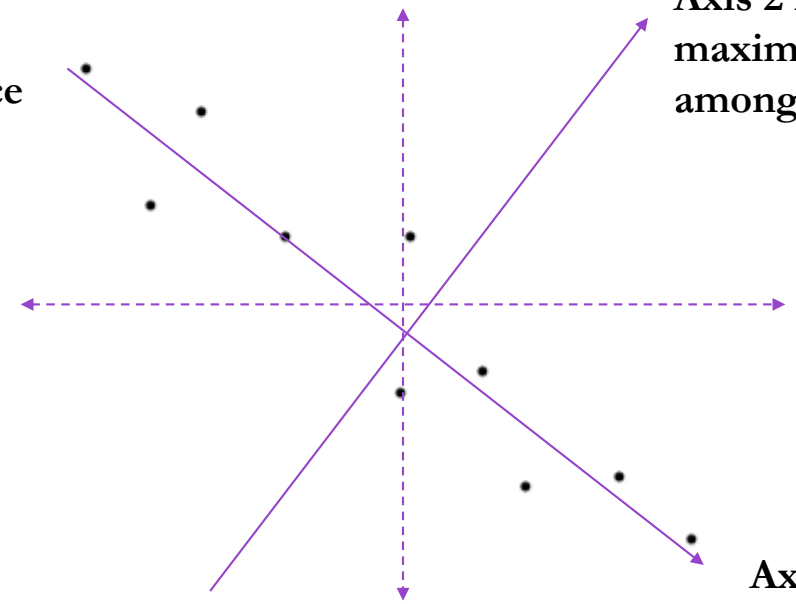


Axis 1 is the axis explaining the max amount of variation

PCA, an intuition

10 points in 2-dimensional space

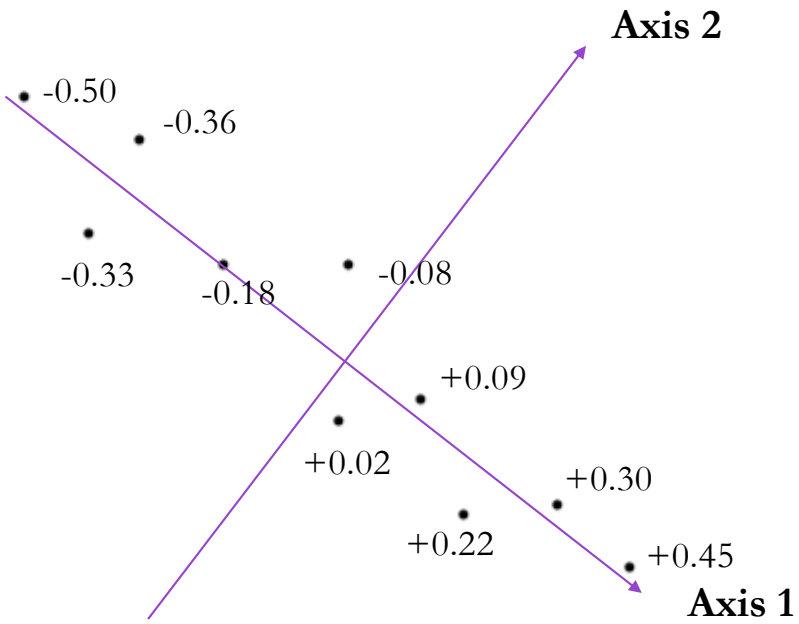


Axis 2 is the axis explaining the maximum amount of variation among axes orthogonal to Axis 1

Axis 1

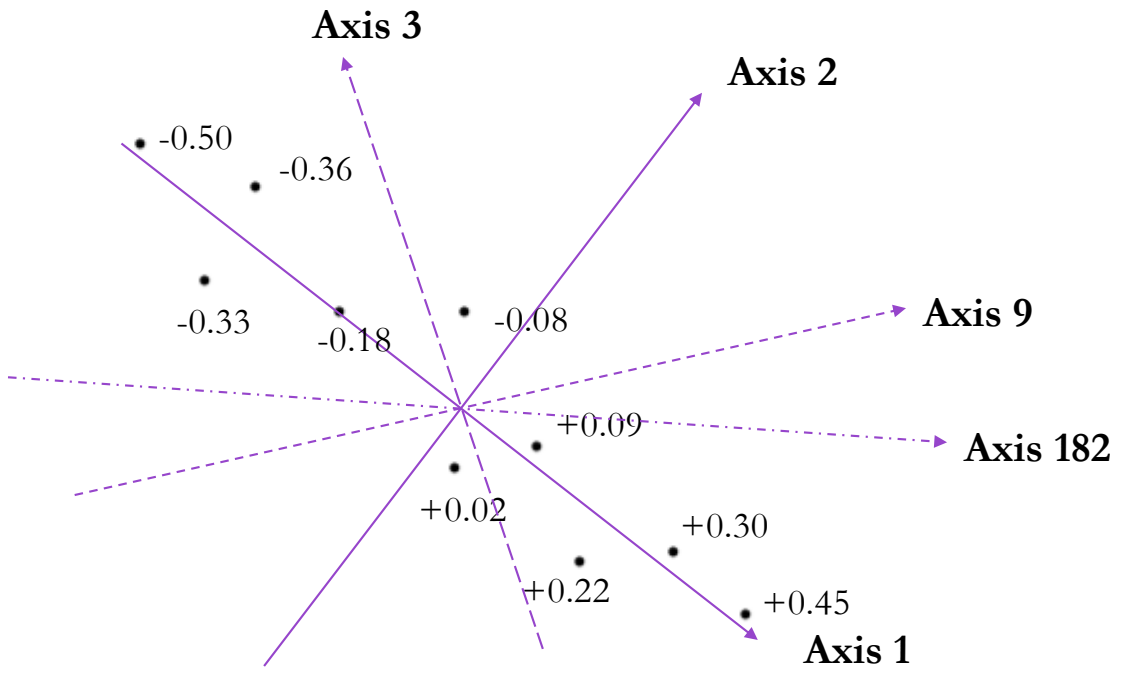
PCA, an intuition

10 points in 2-dimensional space



PCA, an intuition

10 points in 10000-D space



Principal Components Analysis

When applied to genetic data, it can be used to explain differences among individuals. The top PCs are viewed as continuous axes of variation that reflect genetic variation due to (usually) geographical ancestry in the sample.

Individuals with similar values for a particular top PC will have similar ancestry for that axes.

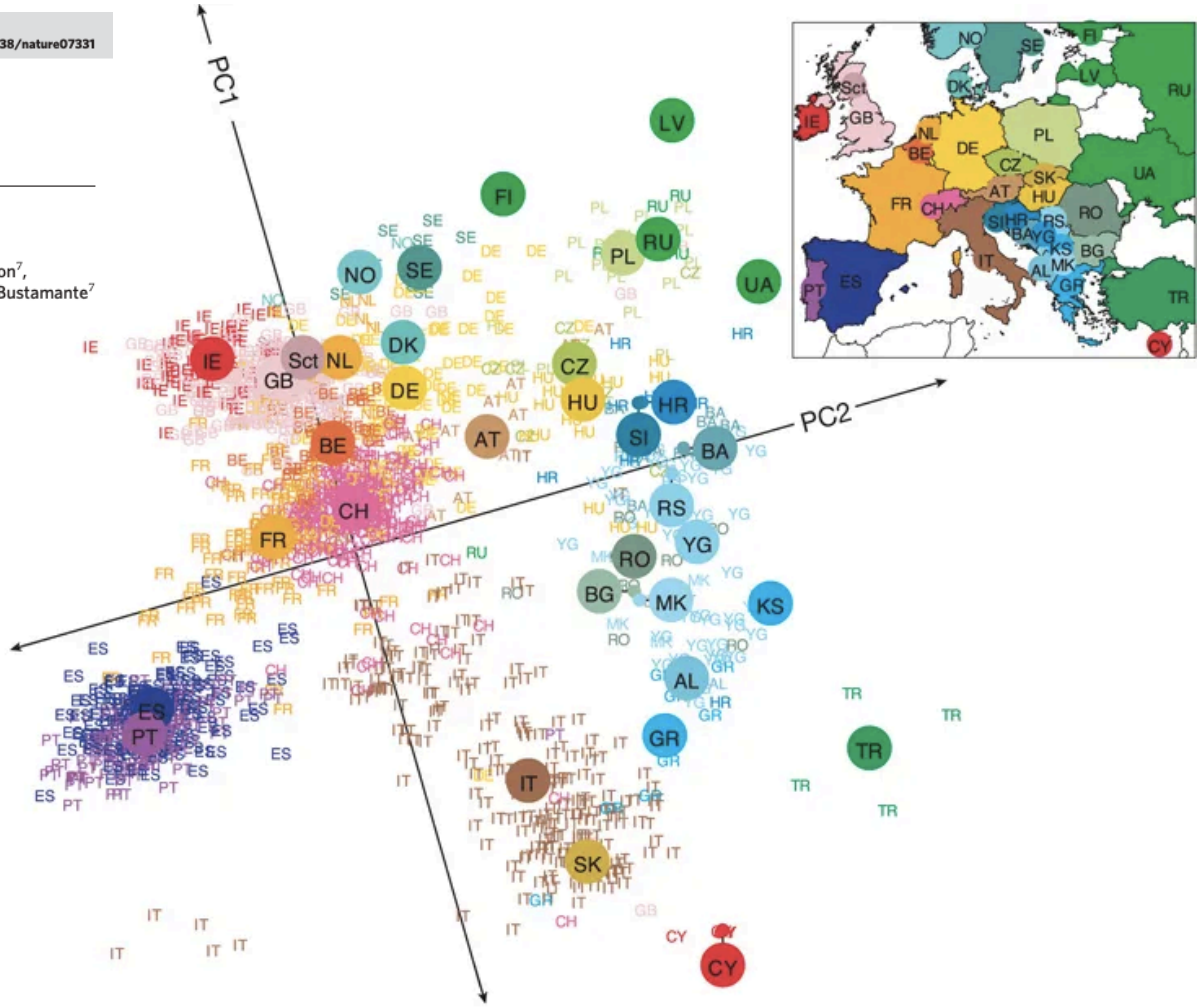
nature Vol 456|6 November 2008|doi:10.1038/nature07331

LETTERS

Genes mirror geography within Europe

John Novembre[1,2], Toby Johnson[4,5,6], Katarzyna Bryc[7], Zoltán Kutalik[4,6], Adam R. Boyko[7], Adam Auton[7], Amit Indap[7], Karen S. King[8], Sven Bergmann[4,6], Matthew R. Nelson[8], Matthew Stephens[2,3] & Carlos D. Bustamante[7]

1,387 Europeans in POPRES dataset
Affymetrix 500K array



Comprehensive Map of Genetic Variation in Han Chinese · doi:10.1093/molbev/msy170 MBE

A Comprehensive Map of Genetic Variation in the World's Largest Ethnic Group—Han Chinese

Charleston W.K. Chiang,*[1,2] Serghei Mangul,[3,4] Christopher Robles,[5] and Sriram Sankararaman[3,5]
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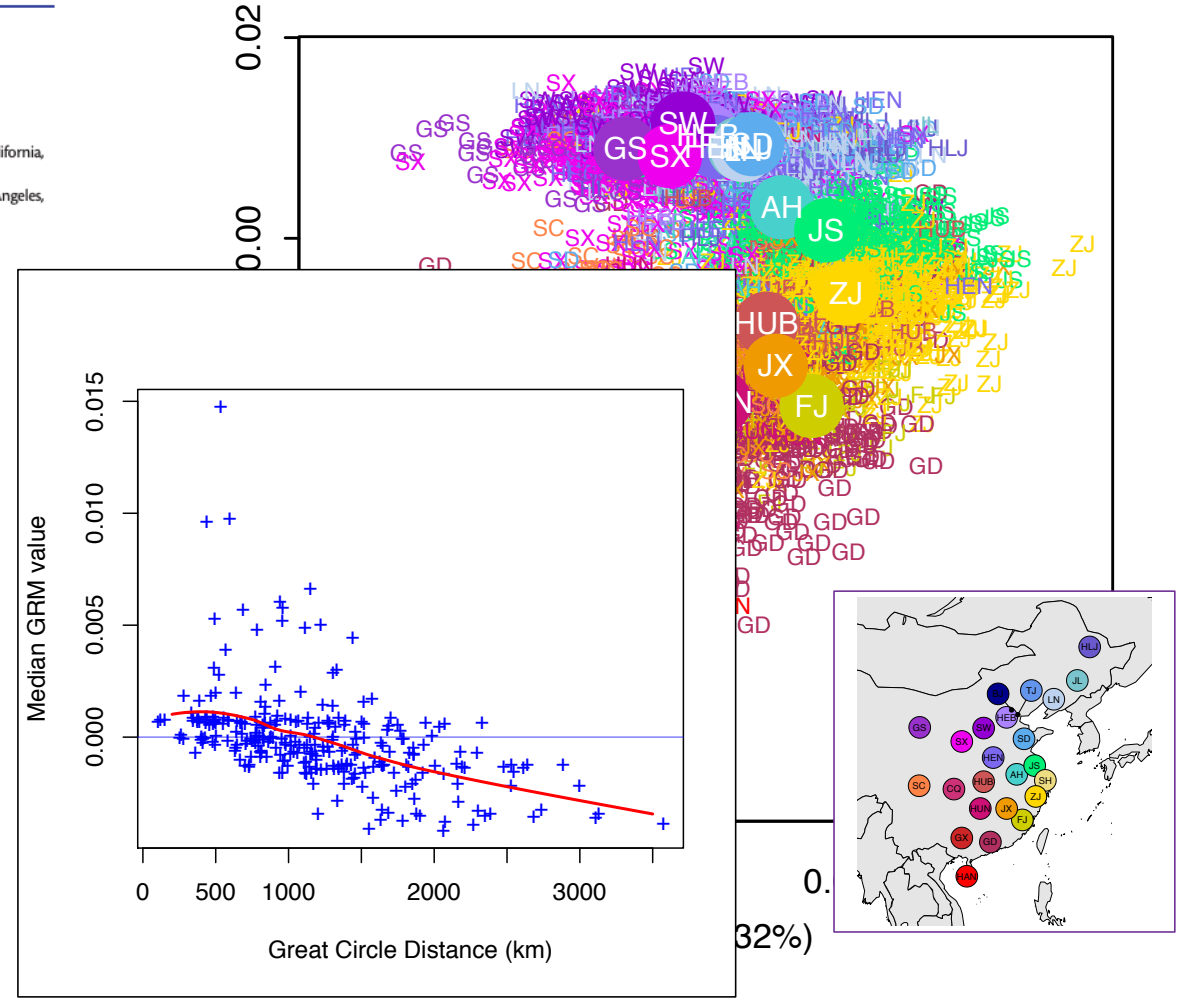
[2]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA
[3]Department of Computer Science, University of California Los Angeles, Los Angeles, CA
[4]Institute for Quantitative and Computational Bioscience, University of California Los Angeles, Los Angeles, CA
[5]Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA
*Corresponding author: E-mail: charleston.chiang@med.usc.edu.
Associate editor: Connie Mulligan

7,457 Han Chinese from 19/22 provinces
1-2x low coverage WGS data

Continuous cline corresponding to geography
PC1 correlated with latitude (r = 0.88)
PC2 correlated with longitude (r = 0.70)

Consistent with isolation-by-distance:
Populations closer to each other geographically have higher genetic similarities



PCs do not necessarily reflect geography, or even population structure …

Batch effects (see Clayton et al. Nat. Genet. 2005; Price et al. Nat. Genet. 2006)

Cryptic relatedness (see Patterson et al. 2006 PLoS Genet.)

Long-range LD, e.g. due to inversion polymorphisms (see Tian et al. 2008 PLoS Genet., Price et al. AJHG 2008)

Really quick word on haplotype-based clustering

Allele frequency-based approach ignores linkage information and treating each marker in analysis as independent (usually pruning to quasi-independent subset). Haplotypes can be more informative for clustering.

E.g. chromopainter and fineSTRUCTURE (Lawson et al. PLoS Genet. 2012)

Down-side is that usually haplotype-based approach is computationally intensive, thus not scalable to the sizes of datasets these days. Works best for < 2,000 individuals.

- But this is active area of development, with promise! (e.g. pBWT, Durbin, Bioinformatics 2014)

Population Genetic forces that shaped genetic variation

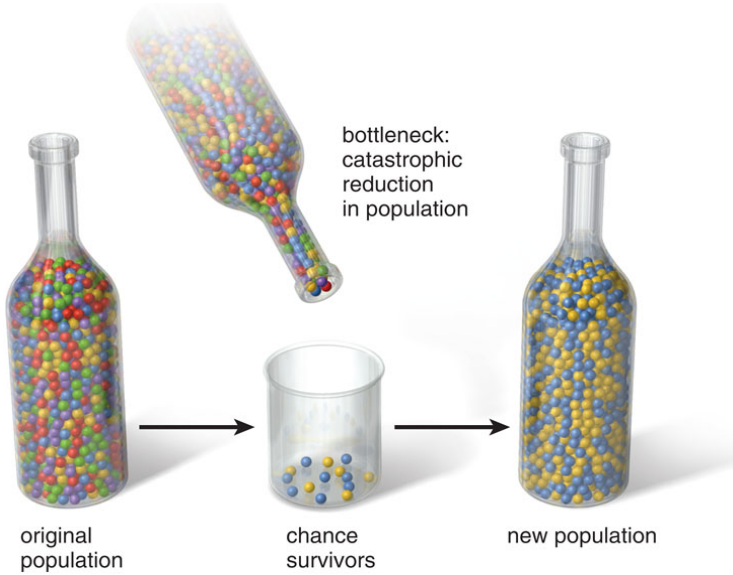
Demographic history

- ~~Population structure~~
- Bottleneck
- Admixture

Natural Selection

Population bottleneck

Population bottleneck is an event that drastically reduces the size of a population

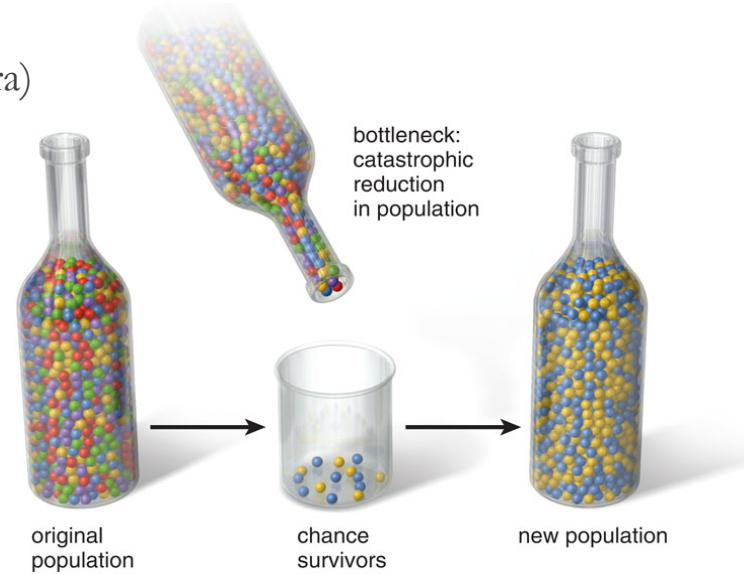


Population bottleneck

Population bottleneck is an event that drastically reduces the size of a population

It could occur by…

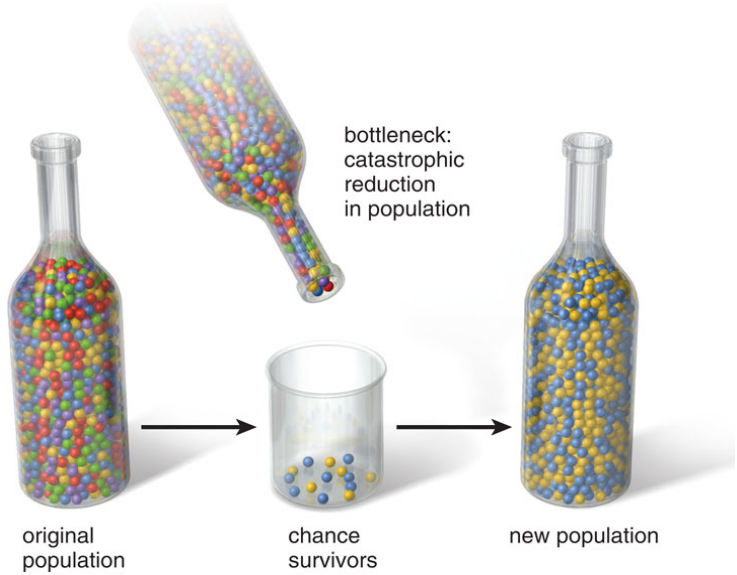
- "Environmental" disasters (Native Americans during colonial era)
- Founding event of a new population (Finland)



What are the impact due to bottleneck?

Population bottleneck decreases the diversity of the gene pool, because many alleles in the parental populations would be lost.

Because of limited number of surviving lineages through a bottleneck, there will be increased LD (e.g. out-of-Africa event, founding of Finland).



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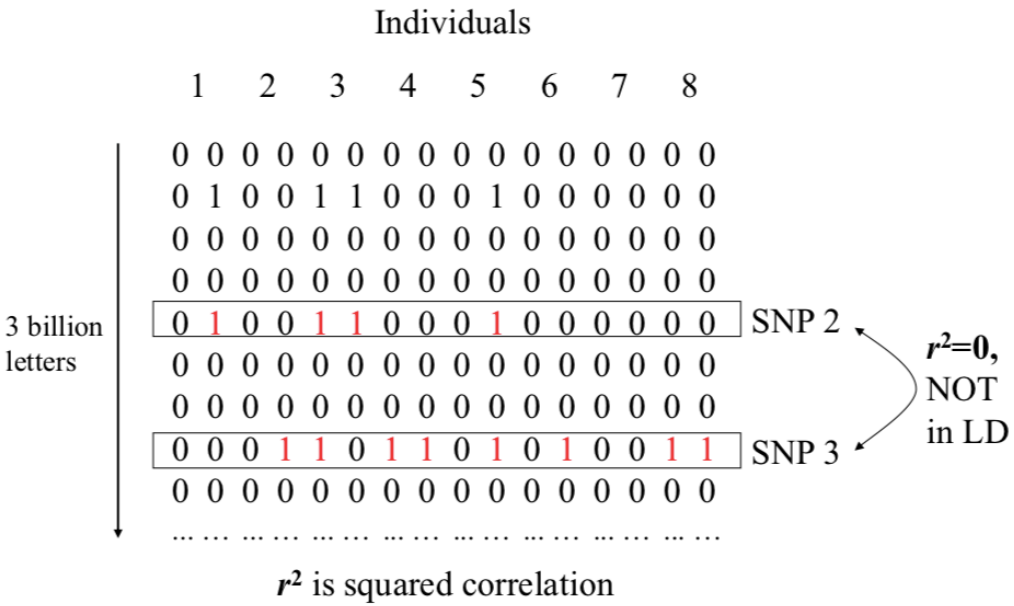

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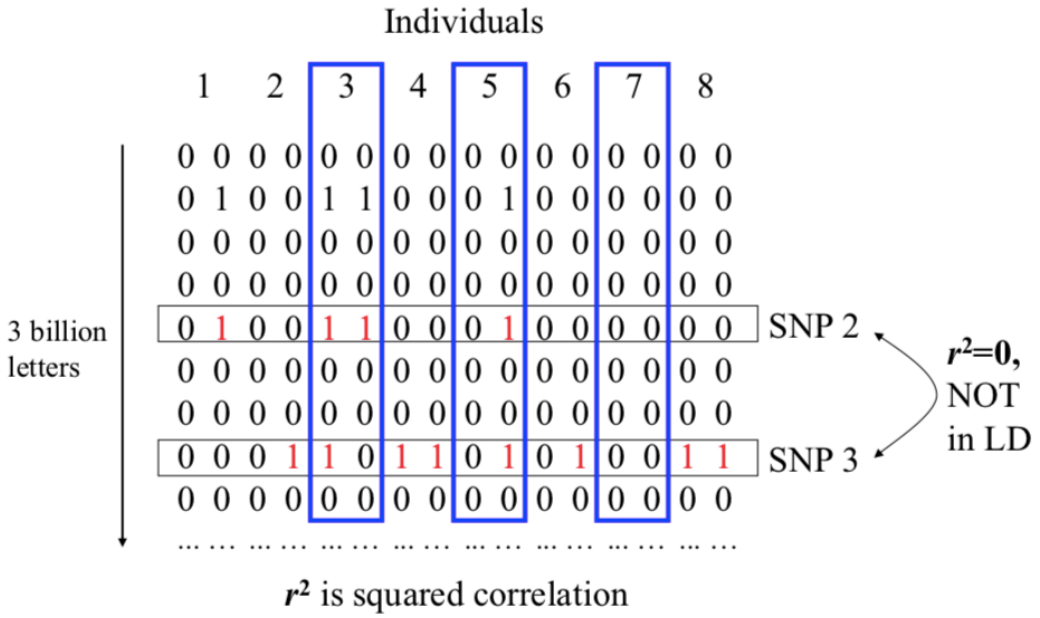

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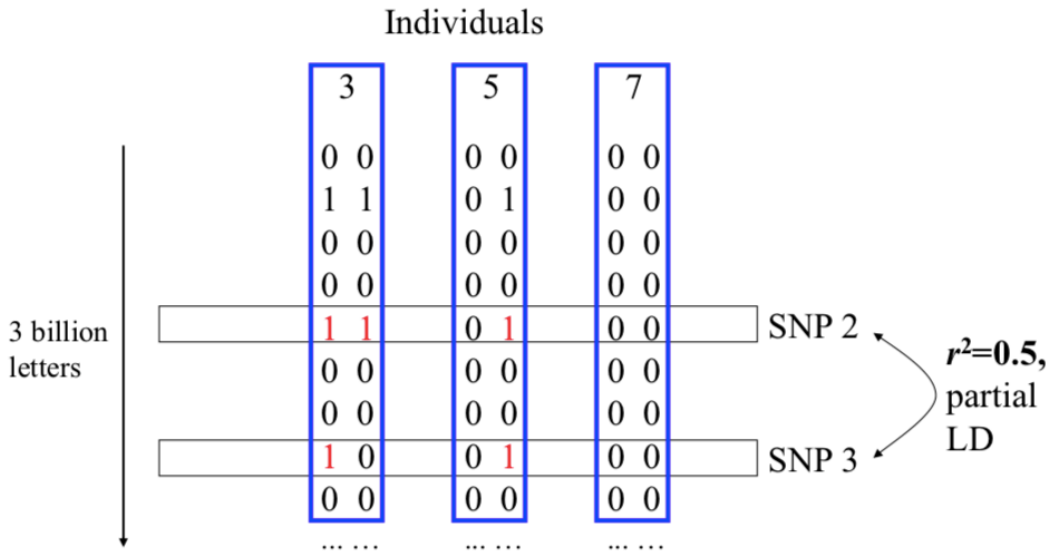

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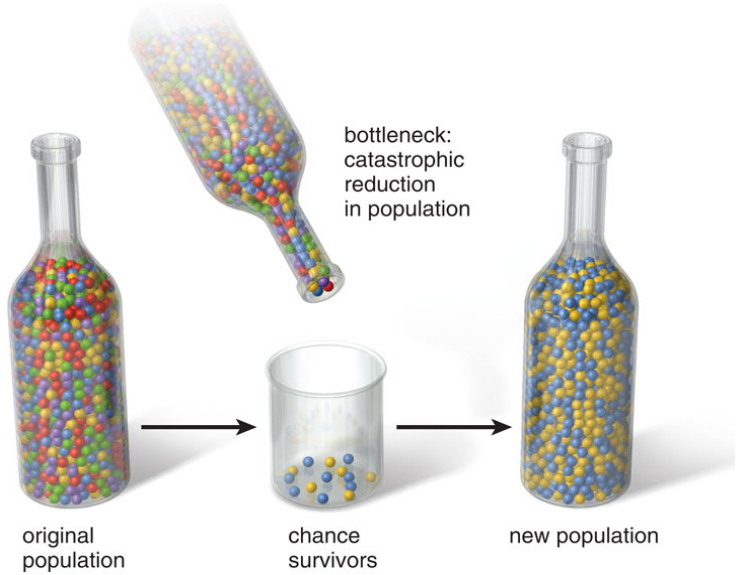
Because of small population sizes, the impact of genetic drift* would increase, causing some rare alleles to elevate in frequency by chance.

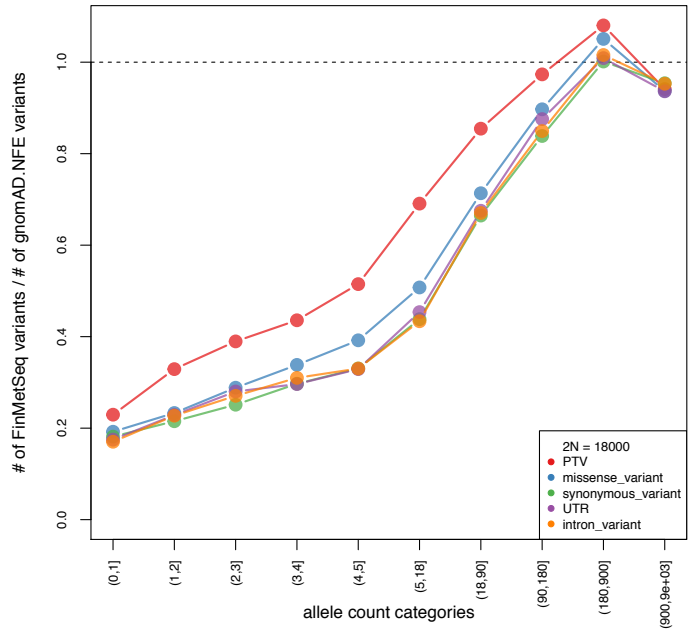


Enrichment of (deleterious) alleles

Because of small population sizes, the impact of **genetic drift*** would increase, causing some rare alleles to elevate in frequency by chance.

- Genetic drift is the random fluctuation of frequency of alleles due to sampling alleles across generations.
- In a smaller population, the sampling error is larger, hence frequencies can change more drastically.

Compared to a larger population, the enrichment would be more pronounced for deleterious alleles that would otherwise be negatively selected against.



Locke*, Steinberg*, Chiang*, Service* et al., Nature 2019

Population Genetic forces that shaped genetic variation

Demographic history

- ~~Population structure~~
- ~~Bottleneck~~
- Admixture

Natural Selection

What is an admixed population?

An **admixed population** is a population with "recent" ancestry from two or more continents.

- let's say, within the last ~1000 years, loosely defined.
- Could be used to refer to "ancient admixture", or "archaic admixture", like with Neandertals

What is the difference between population **structure** and population **admixture**?

Structure is genetic differences due to geographic ancestry. We are usually interested to use genome-wide data to infer broader scale cluster membership.

Admixture is mixed ancestry from multiple continental populations. We are usually interested to infer local ancestry at each location in the genome.

Population admixture implies population structure; population structure does not imply population admixture.

What are some examples of admixed populations (in U.S. or around the world)?

African Americans

- African and European ancestry; > 10% of U.S. population

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Latino Americans

- European, Native American, and African ancestry; >15% of U.S. population
- e.g. Mexican Americans, Puerto Ricans, etc.
- Hundreds of millions of people throughout Latin America

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Native Hawaiians

- Polynesian, European, and East Asian ancestry

Uyghurs

- East Asian and European-related ancestry

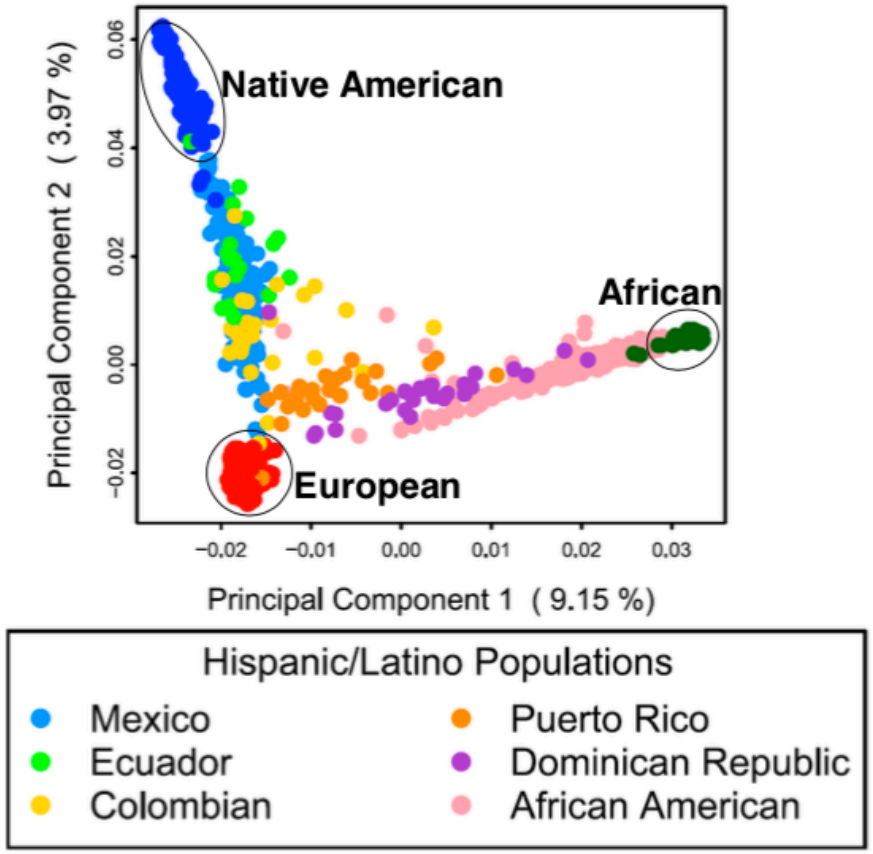
Non-Hispanic Whites is currently the majority in U.S. (77.5% in 2014). They are projected to be the only 43.6% in 2060, while multi-race individuals will grow by 219%.

-- U.S. Census Bureau

How to infer genomic ancestry?

Globally

- Apply the clustering programs that allow fractional ancestry (STRUCTURE, FRAPPE, ADMIXTURE, etc.)
- Or, apply PCA. Admixed individuals tend to form a cline between parental populations in PCA space.



	European	Native Am	African
Mexican Americans	~50%	~45%	~5%
Puerto Ricans	~60%	~20%	~20%
Brazilians and Columbians	~70%	~20%	~10%

Within a population, there are substantial variations of the ancestry proportions per individual (the "cline")

Across geographical space (such as U.S.), there are variation of the average ancestry proportion as well.

Estimates are for population sampled and defined. Values may not apply to all populations.

Bryc et al. PNAS 2010

Price et al. AJHG 2007

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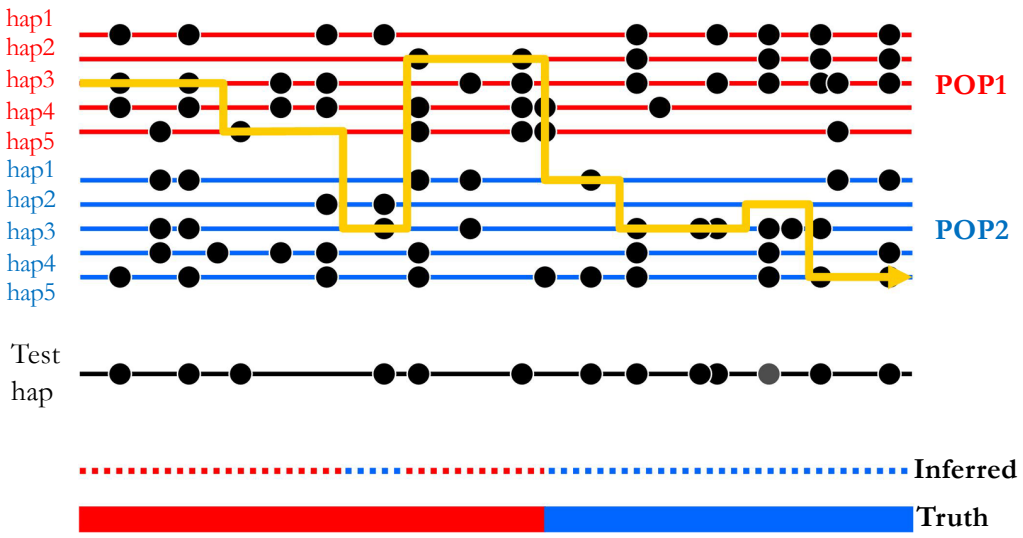
Locally

- Generally supervised approach, i.e. leveraging reference panel of haplotypes assumed to be representative of the ancestral populations.
- *Generative* HMM type of approaches
- *Discriminative* conditional random field type of approaches

Inferring local ancestry via HMM

HAPMIX (Price et al. PLoS Genet. 2009)

- Hidden states are local ancestry AND source haplotype from POP1 or POP2.
- So models both transitions between local ancestry states (Patterson et al. AJHG 2004) and between haplotypes from ancestral reference populations (Li & Stephens, Genetics 2003).
- Given initial, transition, and emission probabilities, use the forward-backward algorithm to infer P(states | data)



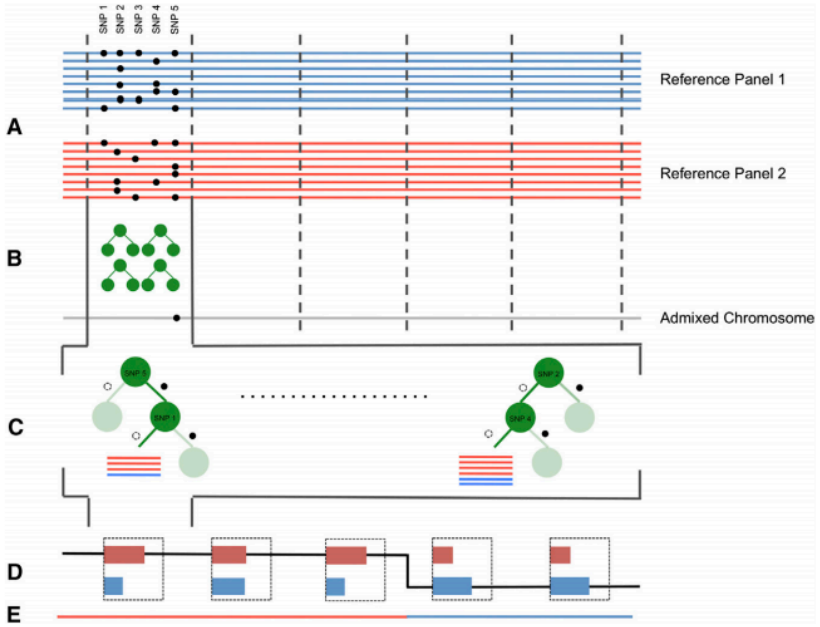
Advantage: really used all information available in GWAS array data, especially by using LD information.
Disadvantage: increased complexity and computationally intensive. Limited to 2-way admixed populations.

Inferring local ancestry via CRF

RFMix (Maples et al. AJHG 2013)

- ”Supervised machine learning”
- Break genome into windows. In each window a random forest is trained to distinguish ancestry in the reference panels.
- Consider the test chromosome, each tree in the random forest generates a fractional vote for each ancestry by following the path through the tree corresponding to the admixed sequence.
- Votes are summed to produce posterior ancestry probabilities and most likely sequence of ancestry.

Much faster, can handle multi-way admixture (> 3)



What are the uses for local ancestry?

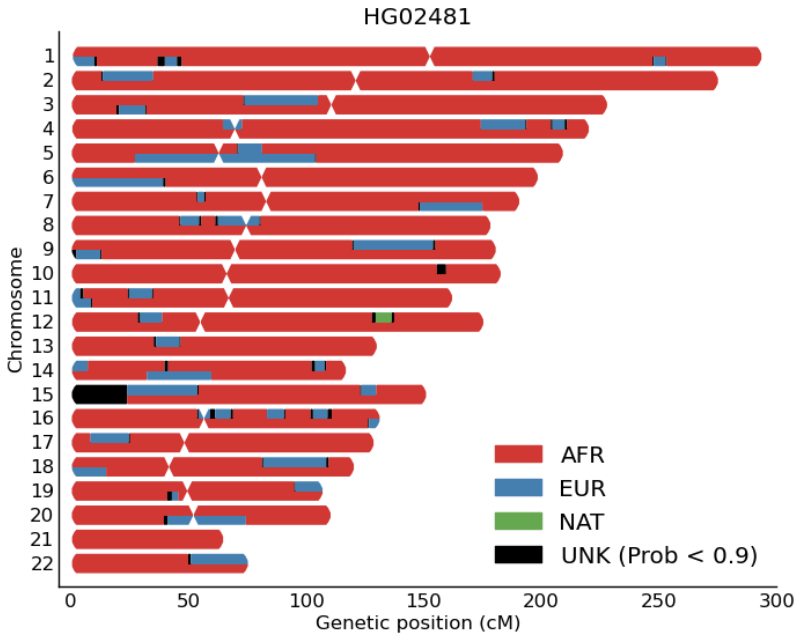
Understanding the demographic history of admixed populations

- Timing of admixture, number of pulses, sex-biased?

Detect adaptive introgression

Admixture mapping to detect disease alleles that might be particularly prevalent in one of the ancestral population.

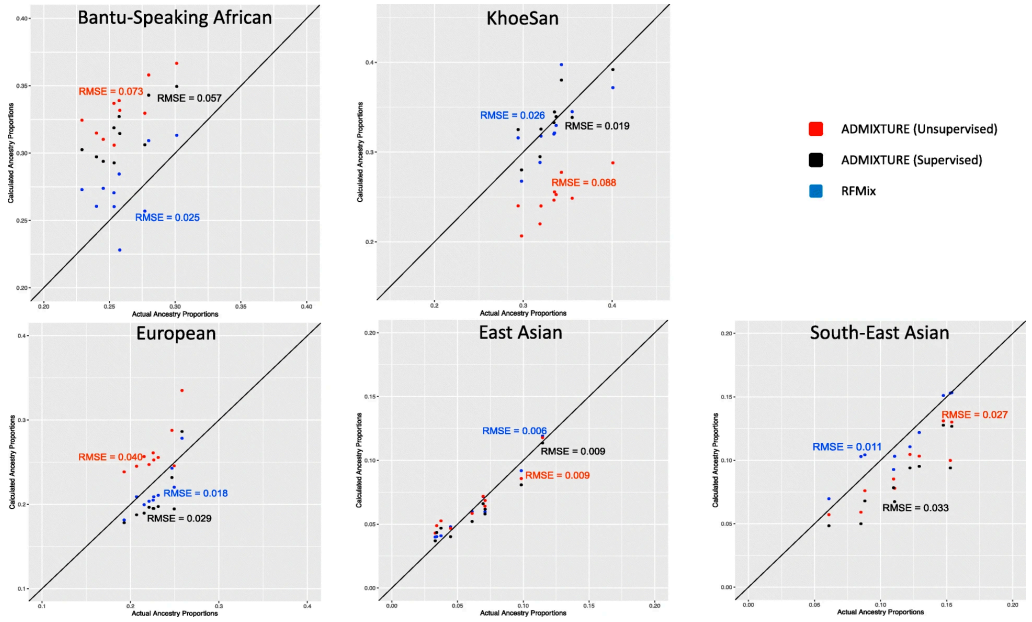
- Particularly since the disease allele does not need to be genotyped – captured by the local ancestry.



https://github.com/armartin/ancestry_pipeline

Be wary with genetic ancestry…

Estimation is not without errors, particularly at the individual level.



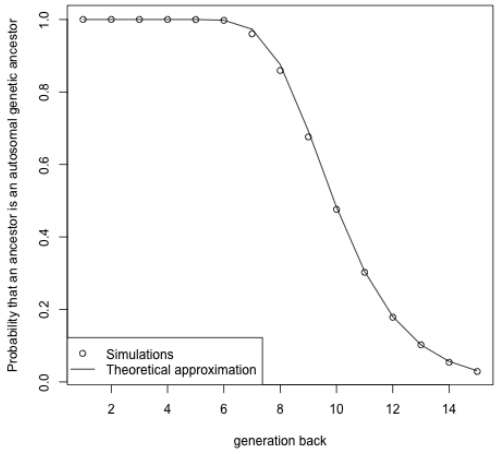
Uren, Hoal, and Möller
BMC Genomics 2020

Be wary with genetic ancestry…

Estimation is not without errors, particularly at the individual level.

There is a conceptual difference between genealogical ancestors and genetic ancestors

- Genealogical ancestors double every generation going back
- Block-like inheritance means you don't inherit genetic material from every single one of them.



https://gcbias.org/2013/11/11/how-does-your-number-of-genetic-ancestors-grow-back-over-time/

Be wary with genetic ancestry…

Estimation is not without errors, particularly at the individual level.

There is a conceptual difference between genealogical ancestors and genetic ancestors.

- Genealogical ancestors double every generation going back
- Block-like inheritance means you don't inherit genetic material from every single one of them.

There are sensitive issues with social, political, and economic consequences of estimating genetic ancestry in indigenous populations.

Genetic ancestry quantization should not supplant current standards (*e.g.* self-identity or genealogical records) to define community memberships.

Population Genetic forces that shaped genetic variation

~~Demographic history~~

- ~~Population structure~~
- ~~Bottleneck~~
- ~~Admixture~~

Natural Selection

Natural Selection

Selection is a powerful force of evolution, and comes in many forms. Ultimately though, it acts on an individual's trait or traits to select the fit and remove the unfit.

- What is "fitness"? Survival? Reproductive success?

When the selected trait is heritable in a population, natural selection would impact the **frequencies of alleles** underlying the selected trait.

Types of Selection:

- Positive selection or adaptation
- Negative or purifying selection
- … and others, depending on whether one categorize by effect exerted on phenotype or genetic diversity.

A quick word on purifying selection

Most *de novo* mutations are deleterious rather than beneficial.

- Estimated **distribution of fitness effect (DFE)** on new mutations in the coding region of the human genome (assuming a European population demography) suggests ~30-33% of mutations are neutral or nearly neutral (~67-70% are deleterious to some extent). (Kim et al. Genetics 2017)

Purifying selection removing deleterious mutations help maintain the long-term stability of optimized biological structure. Purifying selection ensures that frequencies of deleterious alleles are low in the population.

- This contributed to the relationship between MAF and effect size in GWAS.

Purifying selection against a deleterious allele will also remove neutral variation linked to that allele, in what is known as **background selection**.

Adaptation vs. purifying selection

Positive selection is usually thought of in the context of recent and local selective pressure that would work to increase the frequency of beneficial alleles. *i.e.* **adaptation**.

I tend to associate purifying selection with biology, which is shared among all human populations*. Whereas adaptation is more a function of human population, where selective forces differ among populations (due to different environments).

A particular trait could be simultaneously subjected to purifying selection and positive selection (in a particular population around the world).

*BUT, the efficiency of purifying selection could differ between populations, since population size influences the relative impact between drift and selection.

Known examples of human adaptation?

Dairy consumptions

Arctic environment

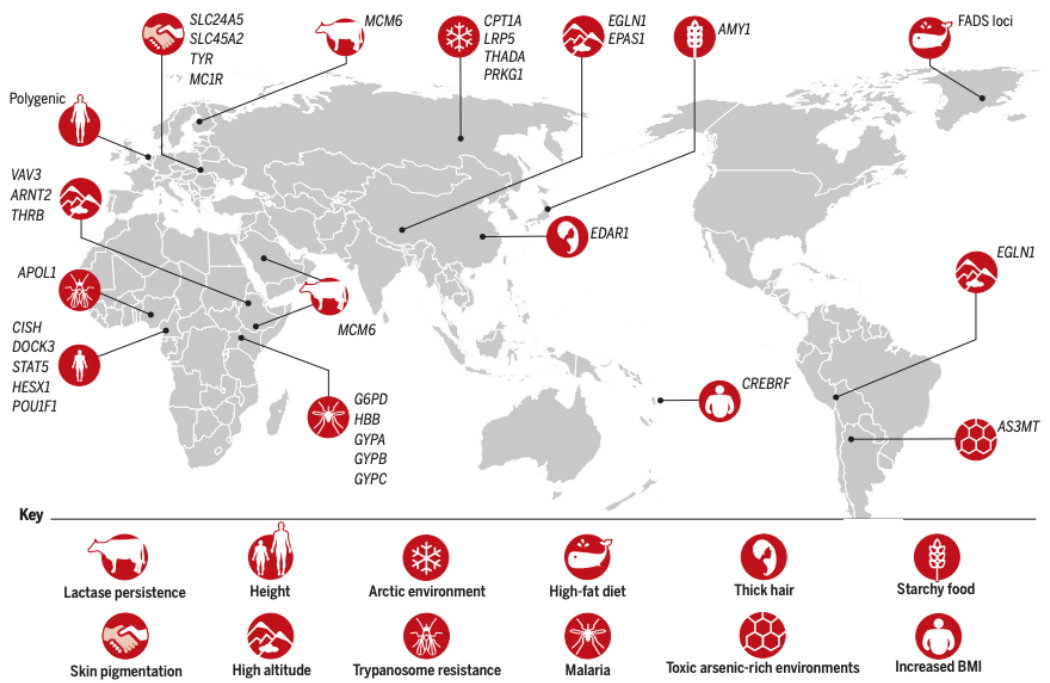
Endemic pathogens

High altitude

Toxic environment

UV exposure

…



Fan et al. Science 2016

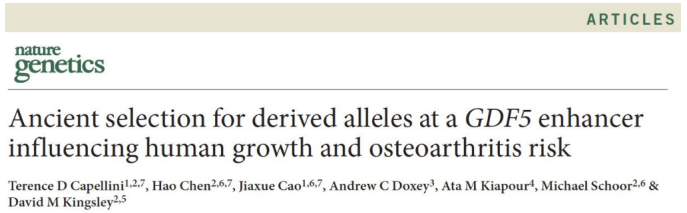
What was adaptative in the past could become maladaptive today and contribute to diseases

GDF5 variant affects bone growth, positively selected in cold climate, but increased arthritis risk.

APOL1 variant protects against African sleeping disease, positively selected in Africa, but increase kidney disease risk.

CREBRF variant lowers energy use and increase adipose storage, positively selected in Samoans, but increase obesity risk.

…

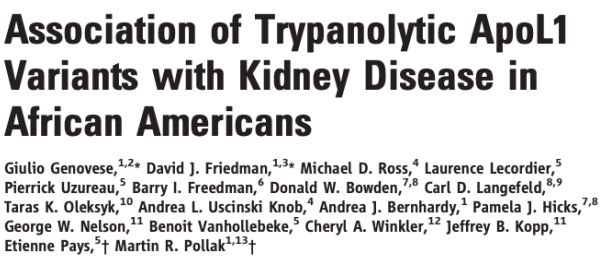


ARTICLES

nature genetics

Ancient selection for derived alleles at a *GDF5* enhancer influencing human growth and osteoarthritis risk

Terence D Capellini[1,2,7], Hao Chen[2,6,7], Jiaxue Cao[1,6,7], Andrew C Doxey[3], Ata M Kiapour[4], Michael Schoor[2,6] & David M Kingsley[2,5]



Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans

Giulio Genovese,[1,2*] David J. Friedman,[1,3*] Michael D. Ross,[4] Laurence Lecordier,[5] Pierrick Uzureau,[5] Barry I. Freedman,[6] Donald W. Bowden,[7,8] Carl D. Langefeld,[8,9] Taras K. Oleksyk,[10] Andrea L. Uscinski Knob,[4] Andrea J. Bernhardy,[1] Pamela J. Hicks,[7,8] George W. Nelson,[11] Benoit Vanhollebeke,[5] Cheryl A. Winkler,[12] Jeffrey B. Kopp,[11] Etienne Pays,[5]† Martin R. Pollak[1,13]†

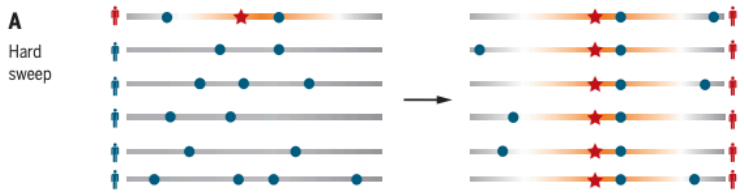
LETTERS

nature genetics

A thrifty variant in *CREBRF* strongly influences body mass index in Samoans

Ryan L Minster[1,13], Nicola L Hawley[2,13], Chi-Ting Su[1,12,13], Guangyun Sun[3,13], Erin E Kershaw[4], Hong Cheng[3], Olive D Buhule[5,12], Jerome Lin[1], Muagututi'a Sefuiva Reupena[6], Satupa'itea Viali[7], John Tuitele[8], Take Naseri[9], Zsolt Urban[1,14], Ranjan Deka[3,14], Daniel E Weeks[1,5,14] & Stephen T McGarvey[10,11,14]

Genomic signature of adaptation

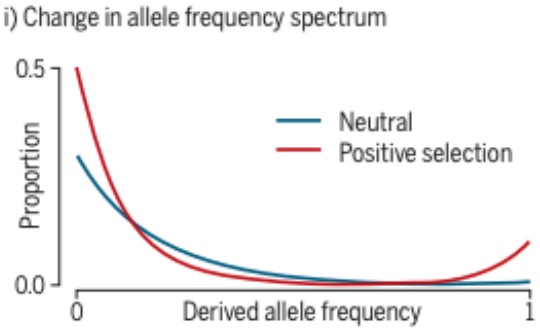


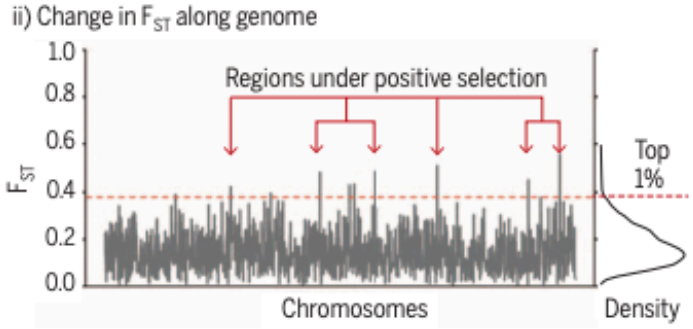
Hard sweep: a new advantageous *de novo* mutation quickly rise in frequency and fix in the population. Neutral variations linked to the advantageous allele will "**hitch-hike**" to higher frequency as well.

Fan et al. Science 2016
Pritchard et al. Curr Bio 2010

Methods to detect recent positive selection

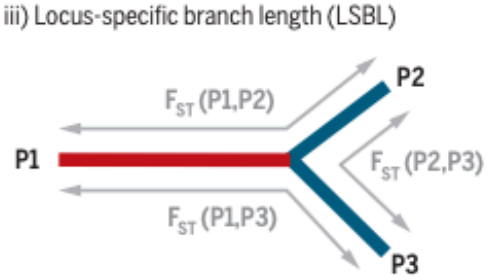
e.g. CLR (Nielsen et al. Genome Res. 2005)

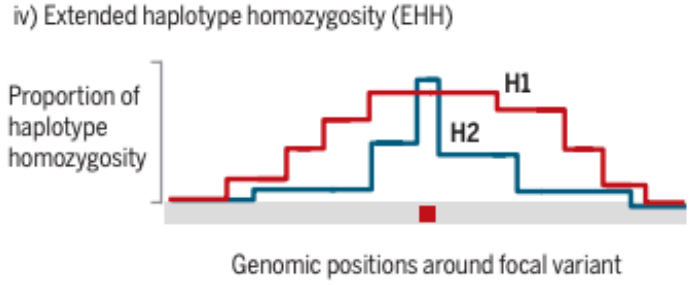




* Fst, between two pops, is equal to the proportion of genotypic variance in each pop attributable to population differences.

e.g. PBS (Yi et al. Science 2010)





e.g. xpEHH (Sabeti et al. Nature 2007), iHS (Voight et al. PLoS Biol 2006), nSL (Ferrer-Admetlla et al. MBE 2014) …

Fan et al. Science 2016

And many more…

Additional haplotype/genealogy-based tests:

SDS (Field et al. Science 2016)

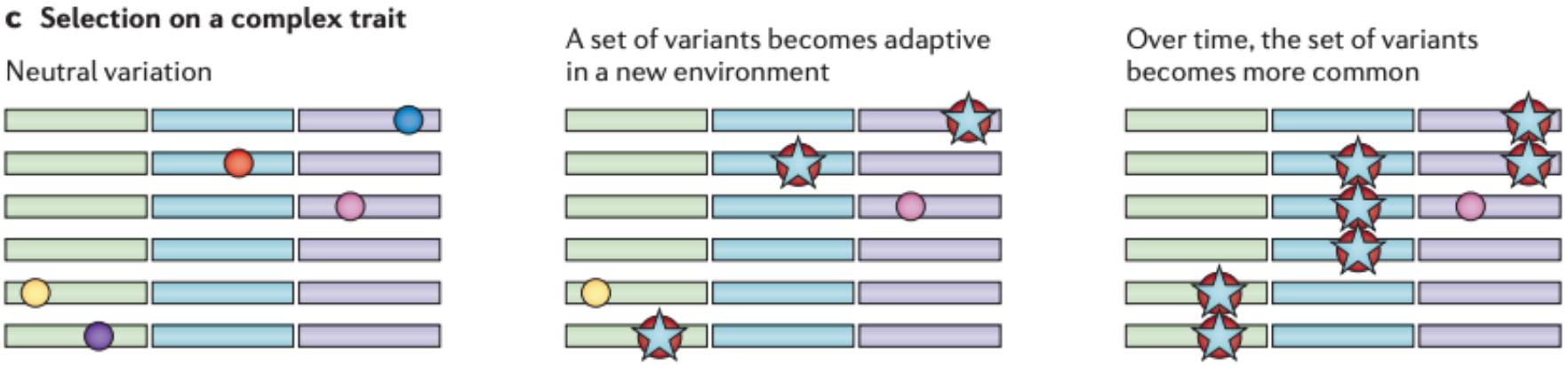
ASMC (Palamara et al. Nat. Genet. 2018)

PRS trajectory (Edge and Coop, Genetics 2019)

Relate (Speidel et al. Nat. Genet. 2019)

…

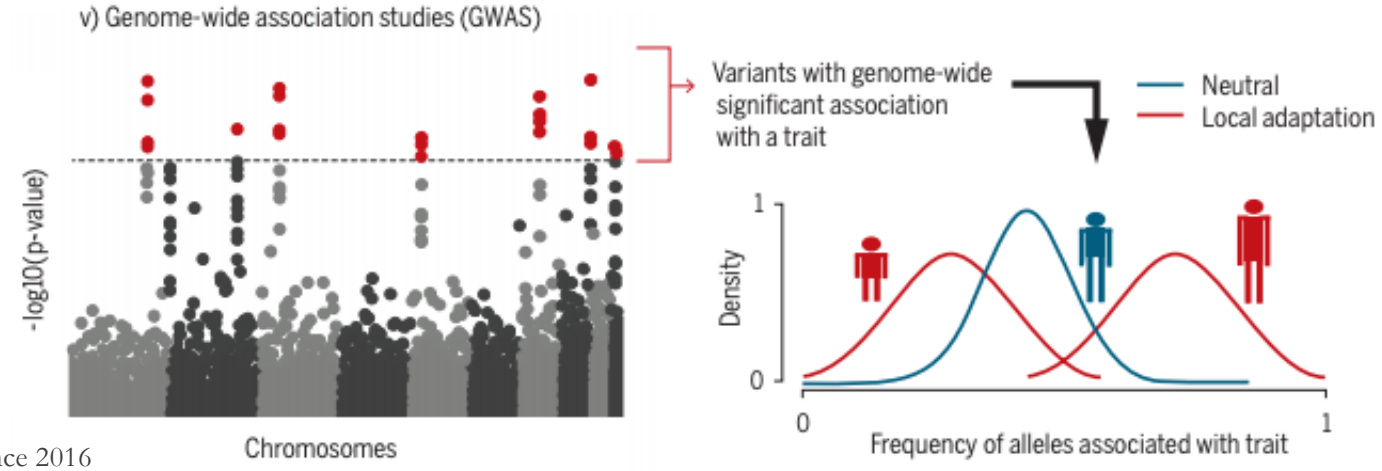
Polygenic adaptation



Pritchard & Di Rienzo, Nat Rev Genet 2010
Pritchard et al. Curr Bio 2010
Scheinfeldt & Tishkoff, Nat Rev Genet 2013

Polygenic adaptation

Haplotypic signature VERY SUBTLE. But we can take a more phenotypic-driven approach and look for concerted directional shift in frequency of GWAS SNPs (e.g. trait-increasing alleles tend to increase in frequency in the taller-trait value population).



Fan et al. Science 2016

e.g. Turchin, Chiang et al. (Nat. Genet. 2012), Berg and Coop (PLoS Genet. 2014), Robinson et al. (Nat. Genet. 2015), Racimo et al. (Genetics 2018) …

Population Genetic forces that shaped genetic variation

- ~~Demographic history~~
  - ~~Population structure~~
  - ~~Bottleneck~~
  - ~~Admixture~~
- ~~Natural Selection~~

Contact and Resources

Any questions or interests in these research themes?

- charleston.chiang@med.usc.edu
- http://chianglab.usc.edu

Other online resources and material (in which this lecture is heavily influenced by):

- https://www.hsph.harvard.edu/alkes-price/epi511/
- https://github.com/cooplab/popgen-notes
- https://github.com/NovembreLab/HGDP_PopStruct_Exercise
- https://github.com/NovembreLab/1000genomes_Selection_Exercise