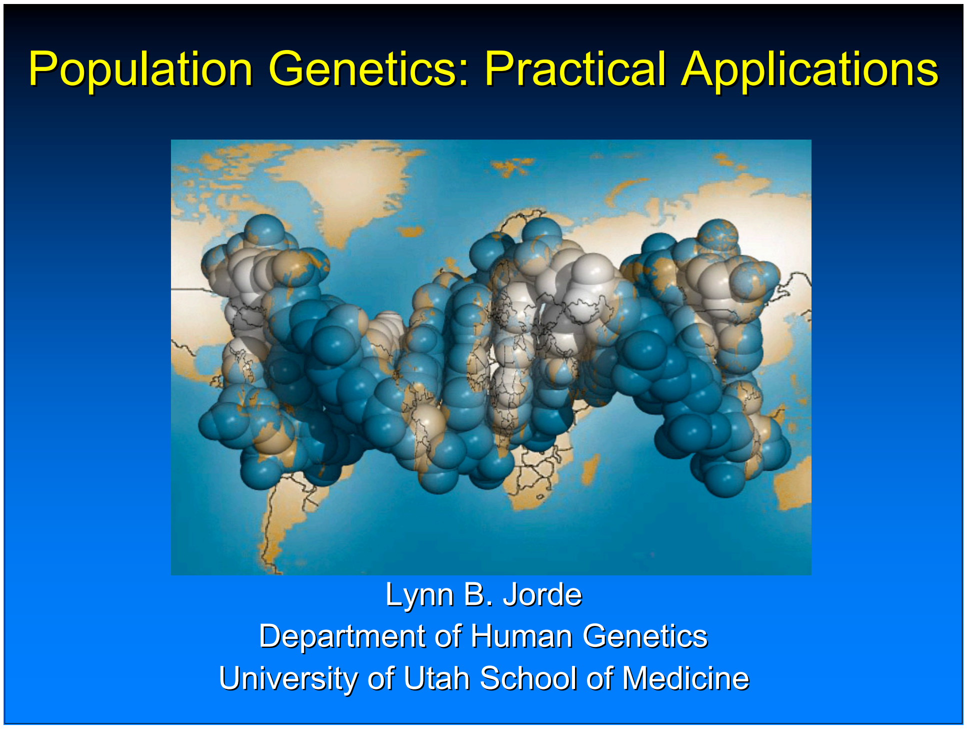
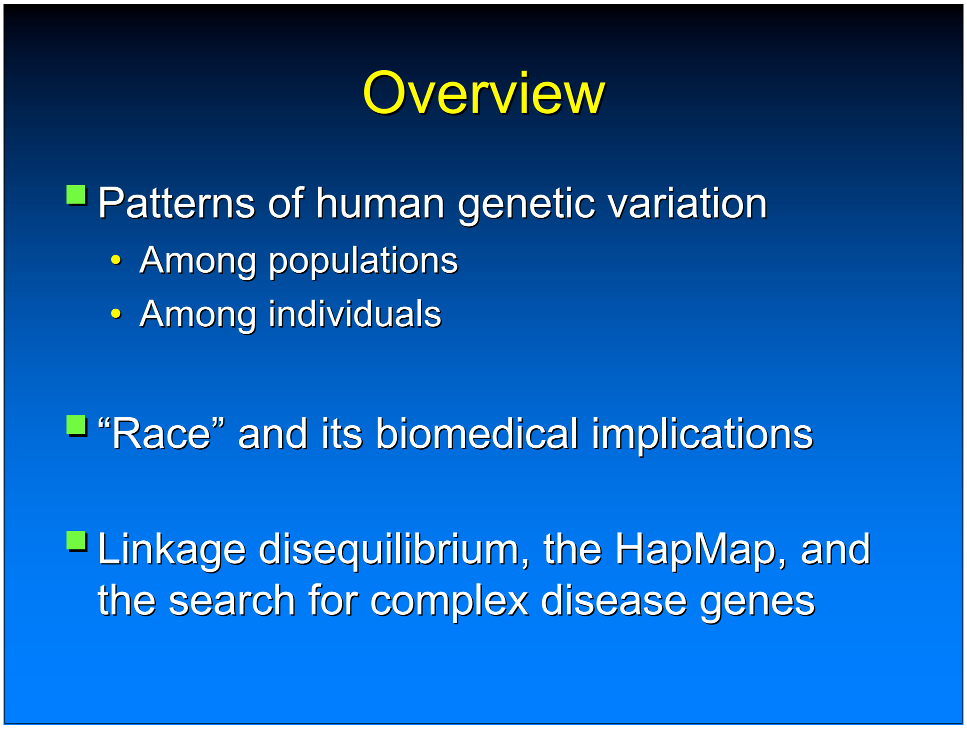


Population Genetics: Practical Applications

Lynn B. Jorde
Department of Human Genetics
University of Utah School of Medicine



Overview

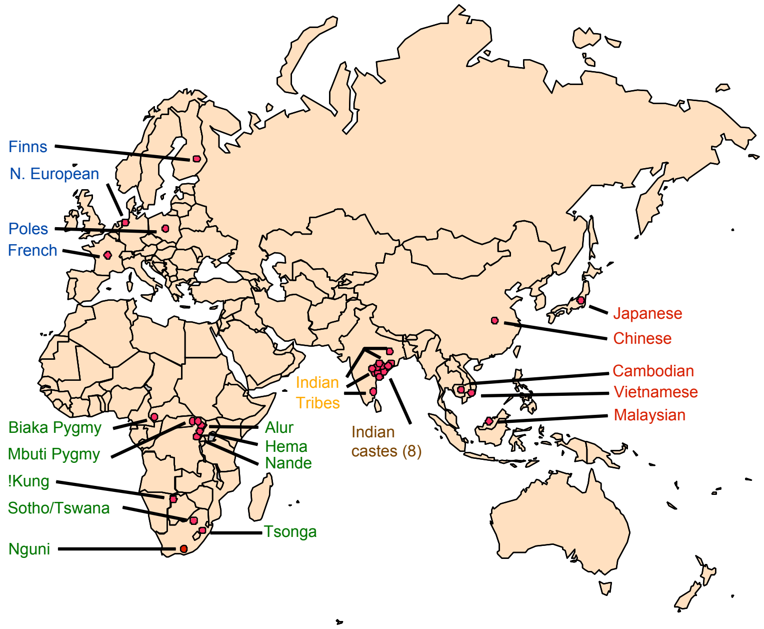
- Patterns of human genetic variation
  - Among populations
  - Among individuals
- “Race” and its biomedical implications
- Linkage disequilibrium, the HapMap, and the search for complex disease genes

Mutation and Genetic Variation

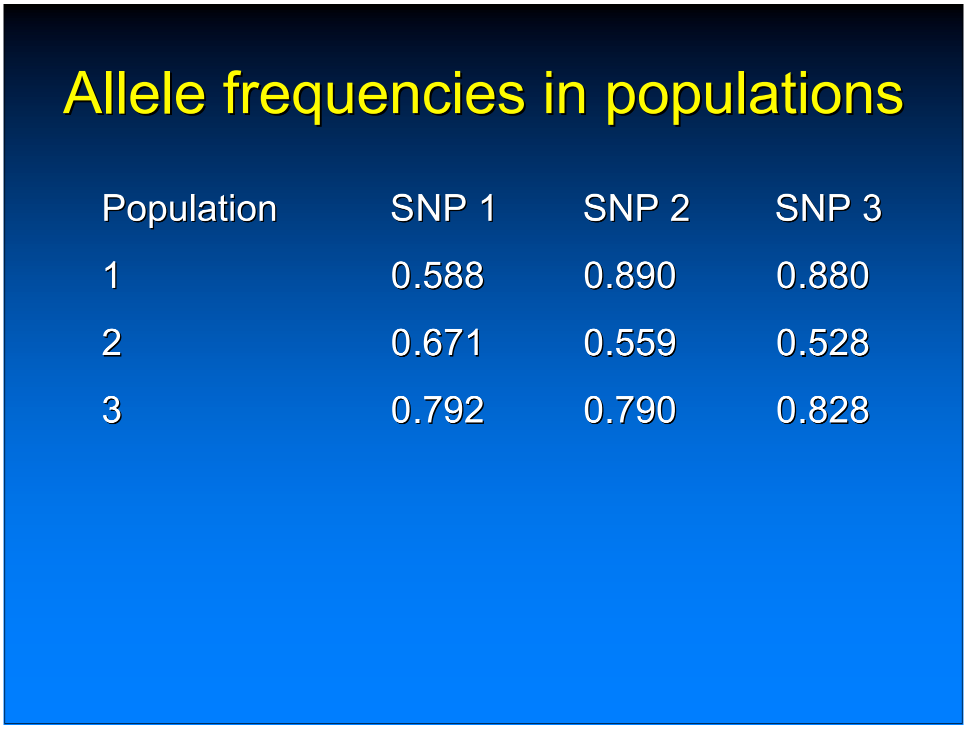
Mutation rate is 2.5 x 10-8 per bp per generation: we transmit 75-100 new DNA variants with each gamete

"The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic bacteria and there would be no music."

- Lewis Thomas

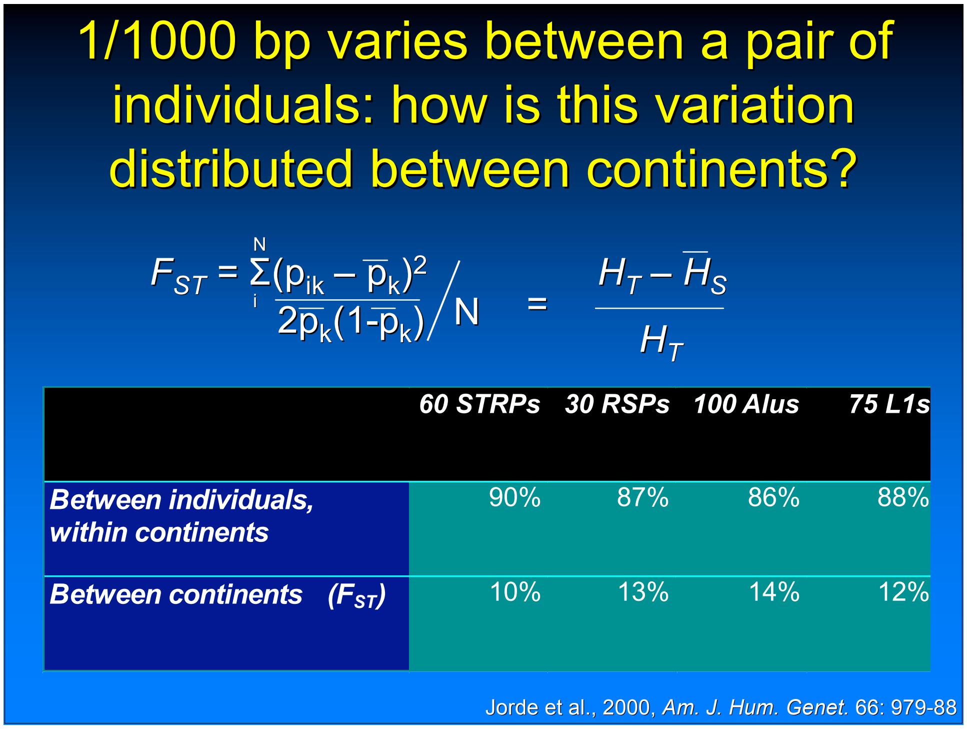


> 250 noncoding loci: *Alu,* LINE1, STR, restriction site polymorphisms, mitochondrial DNA



Allele frequencies in populations

Population	SNP 1	SNP 2	SNP 3
1	0.588	0.890	0.880
2	0.671	0.559	0.528
3	0.792	0.790	0.828

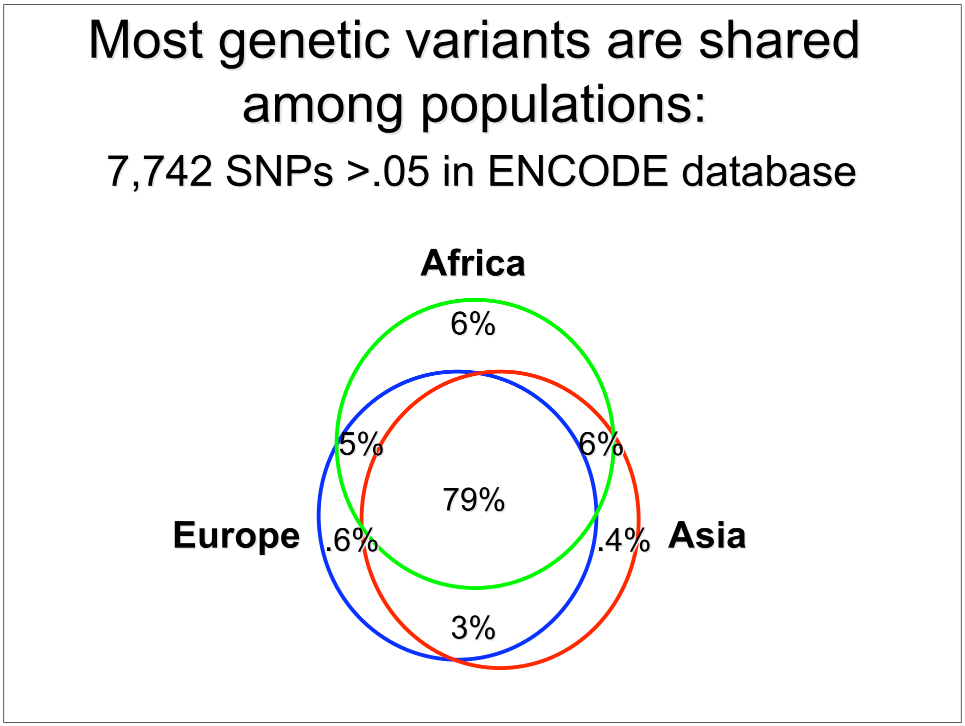


1/1000 bp varies between a pair of individuals: how is this variation distributed between continents?

$$F_{ST} = \sum_{i}^{N} \frac{(p_{ik} - \overline{p}_k)^2}{2\overline{p}_k(1-\overline{p}_k)} \Big/ N \quad = \quad \frac{H_T - \overline{H}_S}{H_T}$$

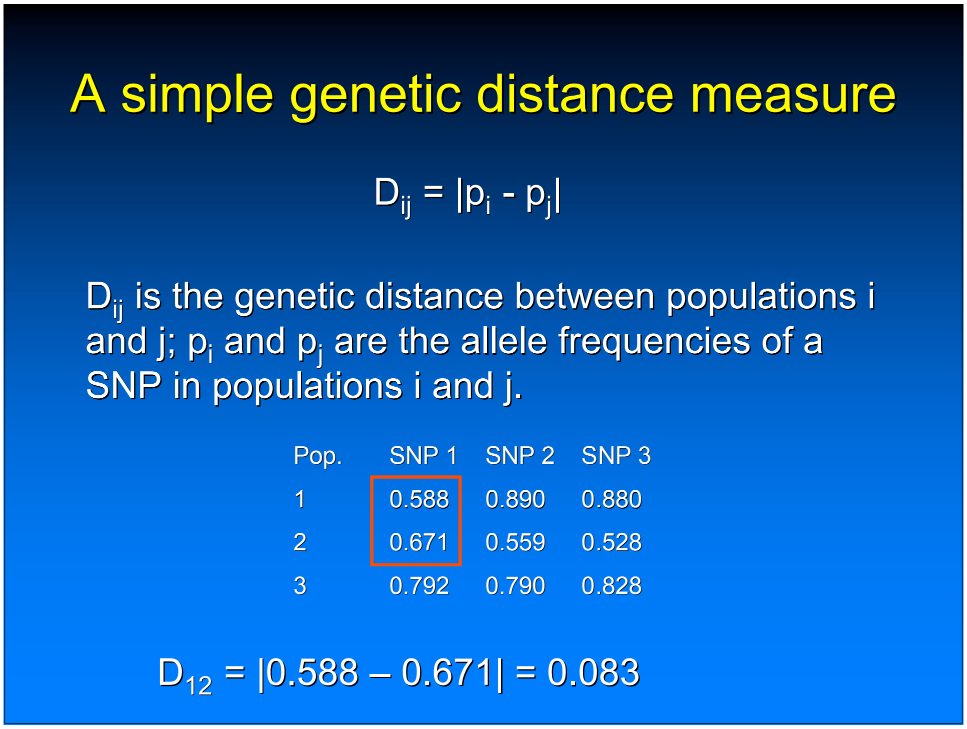
	60 STRPs	*30 RSPs*	*100 Alus*	*75 L1s*
Between individuals, within continents	90%	87%	86%	88%
Between continents (*F_{ST}*)	10%	13%	14%	12%

Jorde et al., 2000, *Am. J. Hum. Genet.* 66: 979-88



Most genetic variants are shared among populations:

7,742 SNPs >.05 in ENCODE database



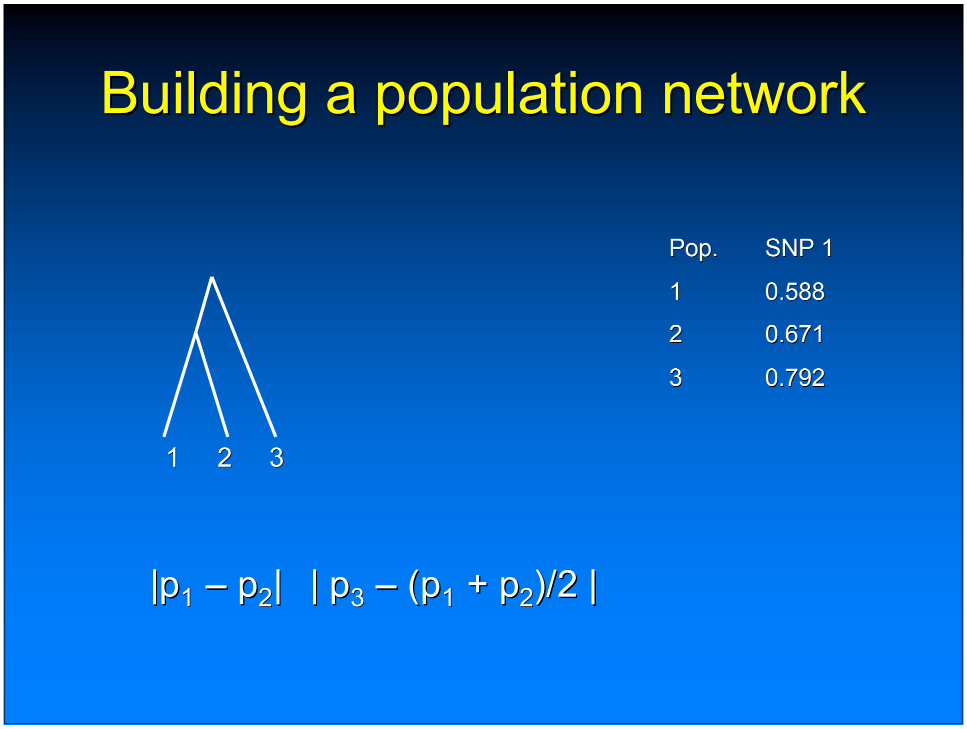
A simple genetic distance measure

$$D_{ij} = |p_i - p_j|$$

D_{ij} is the genetic distance between populations i and j; p_i and p_j are the allele frequencies of a SNP in populations i and j.

Pop.	SNP 1	SNP 2	SNP 3
1	0.588	0.890	0.880
2	0.671	0.559	0.528
3	0.792	0.790	0.828

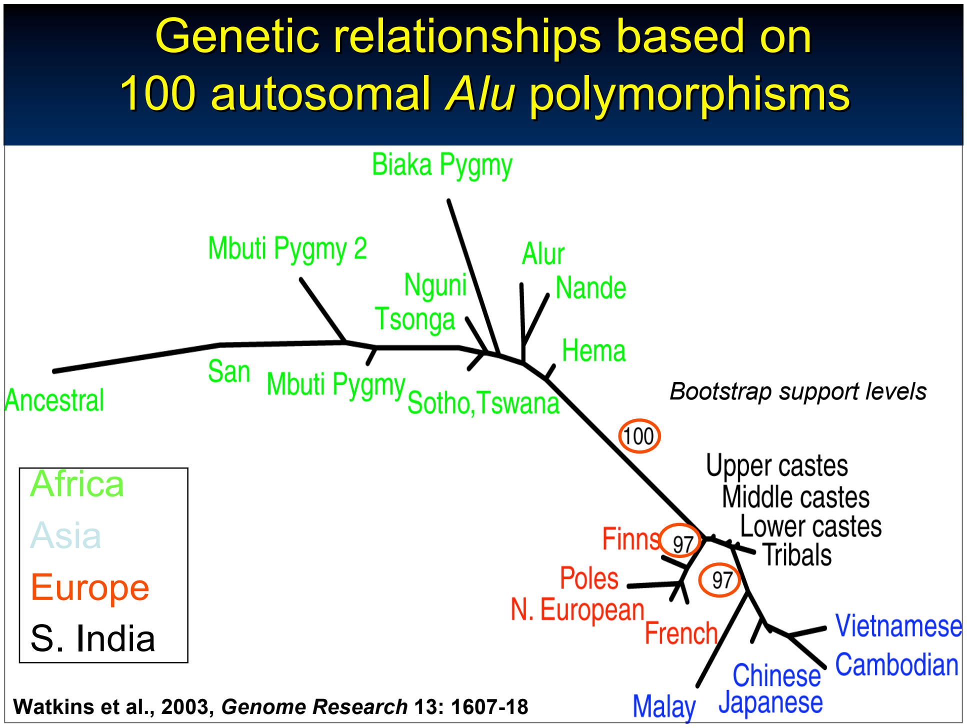
$D_{12} = |0.588 – 0.671| = 0.083$



Building a population network

Pop.	SNP 1
1	0.588
2	0.671
3	0.792

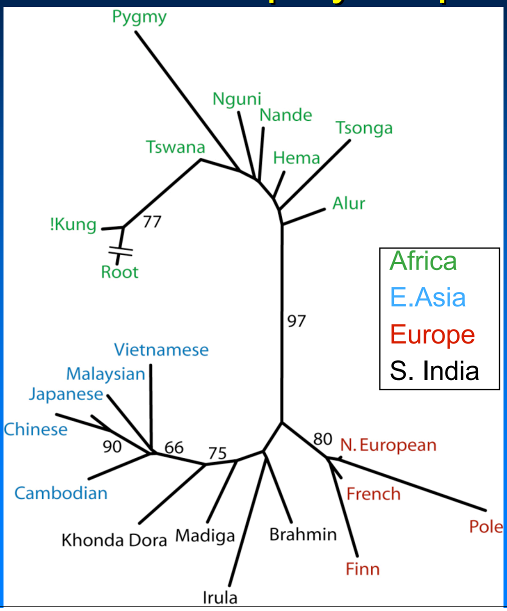
$|p_1 - p_2|$ $| p_3 - (p_1 + p_2)/2 |$



Genetic relationships based on 100 autosomal *Alu* polymorphisms

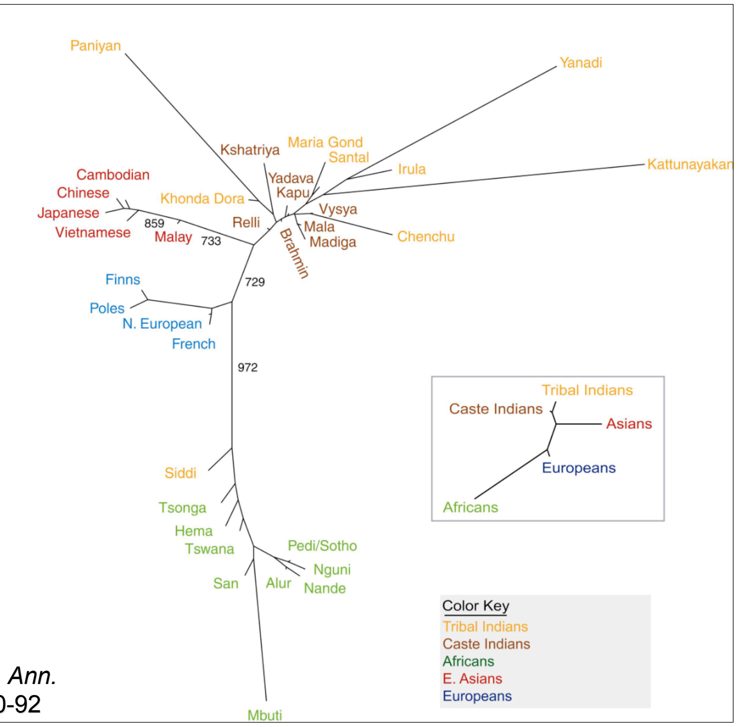
Watkins et al., 2003, *Genome Research* 13: 1607-18

Genetic relationships based on 75 autosomal L1 polymorphisms



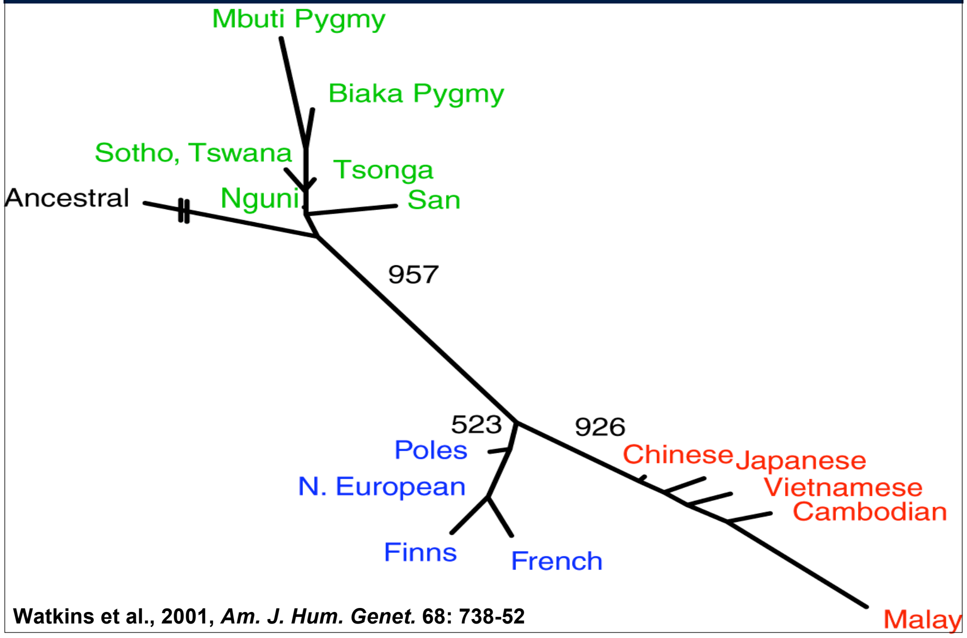
Witherspoon et al., 2006, *Hum. Hered.*, 62: 30-46

45 Autosomal STRs



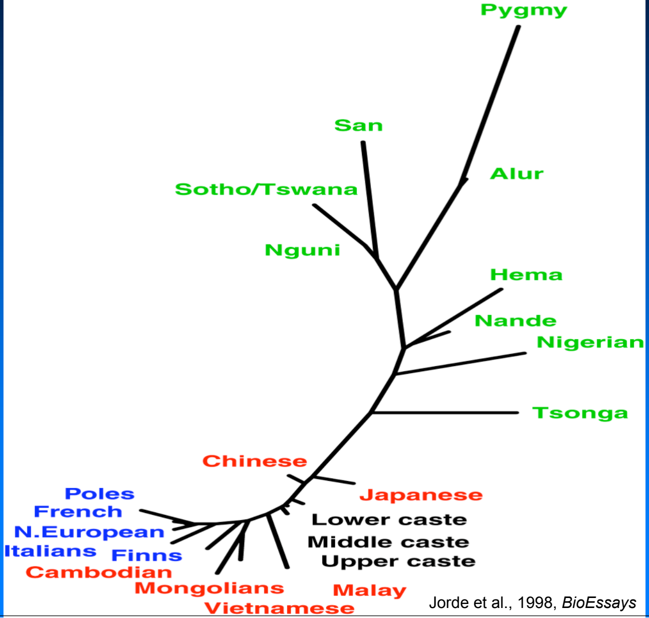
Watkins et al., 2005, *Ann. Hum. Genet.* 69: 680-92

Rooted RSP Tree (30 loci)



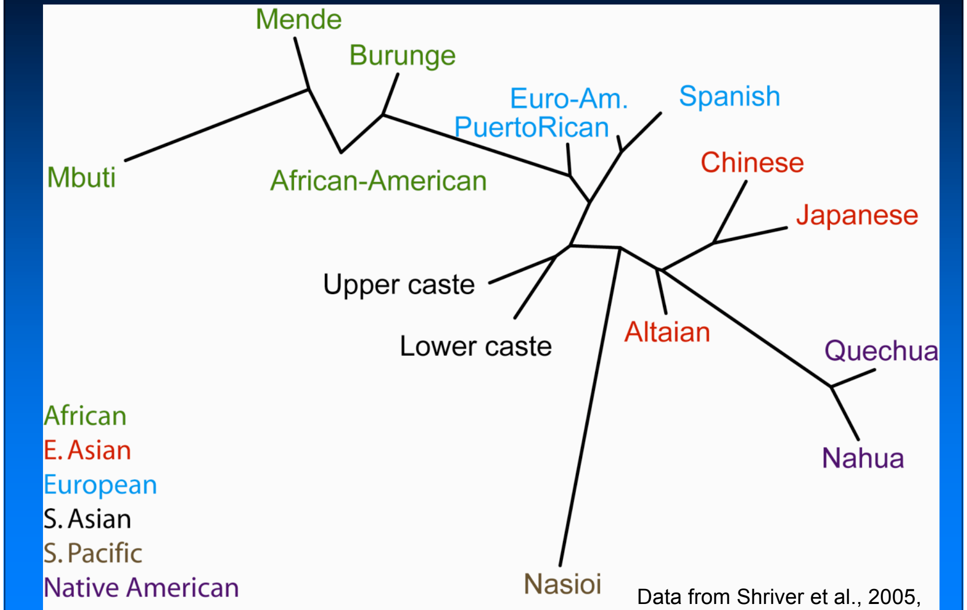
Watkins et al., 2001, *Am. J. Hum. Genet.* 68: 738-52

Mitochondrial DNA (HVS1)

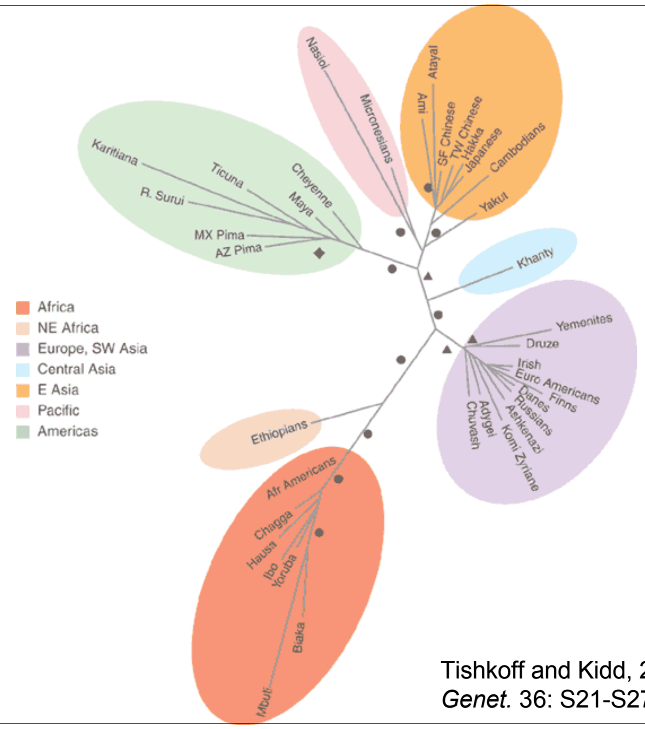


Jorde et al., 1998, *BioEssays*

11,078 SNPs

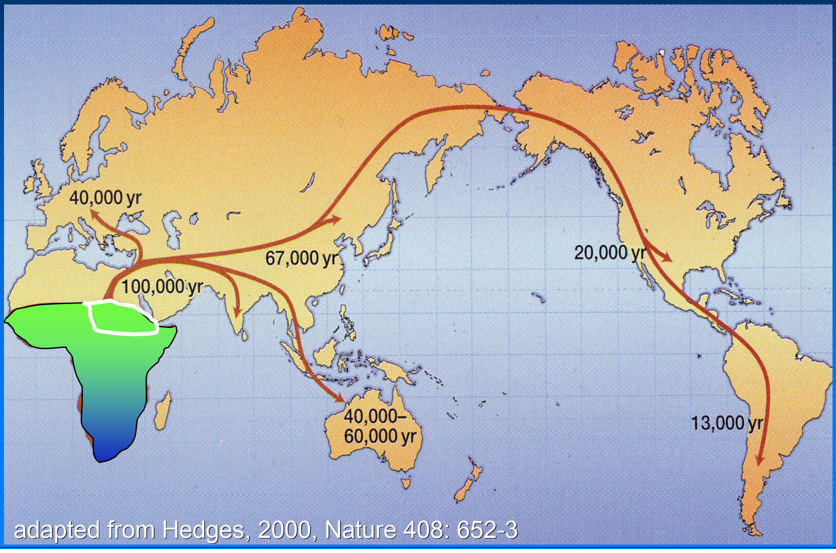


Data from Shriver et al., 2005, *Hum. Genomics* 2: 81-9

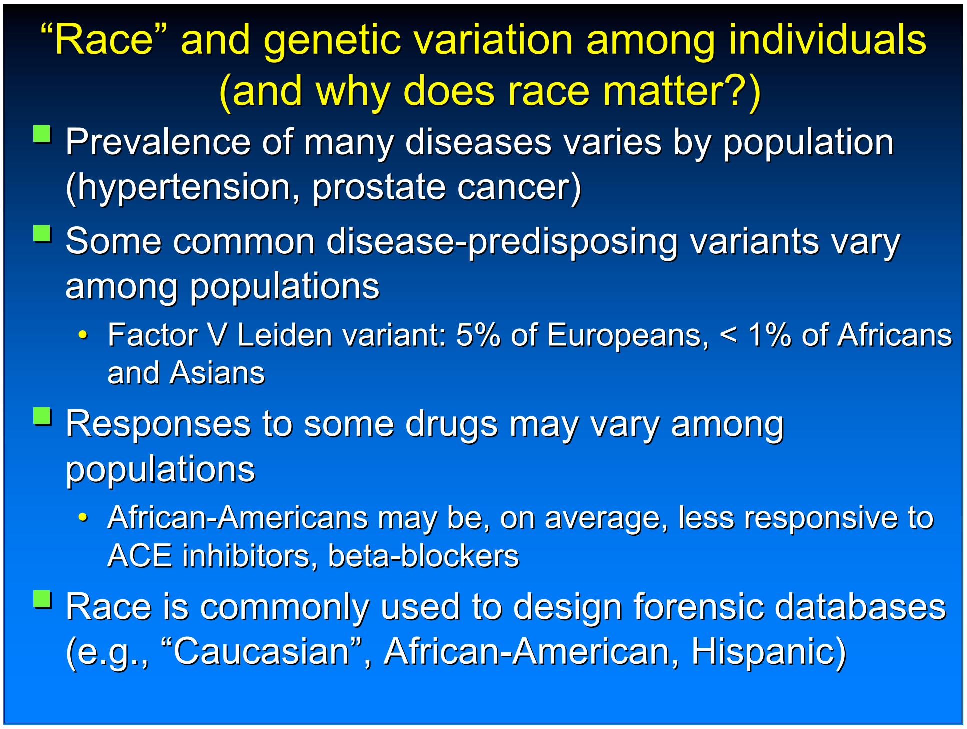


Tishkoff and Kidd, 2004, *Nat. Genet.* 36: S21-S27

Recent African origin of anatomically modern humans



adapted from Hedges, 2000, Nature 408: 652-3



“Race” and genetic variation among individuals (and why does race matter?)

- Prevalence of many diseases varies by population (hypertension, prostate cancer)
- Some common disease-predisposing variants vary among populations
  - Factor V Leiden variant: 5% of Europeans, < 1% of Africans and Asians
- Responses to some drugs may vary among populations
  - African-Americans may be, on average, less responsive to ACE inhibitors, beta-blockers
- Race is commonly used to design forensic databases (e.g., “Caucasian”, African-American, Hispanic)

Recent comments on race

"'Race' is biologically meaningless"
-- Schwartz, 2001, *N. Engl. J. Med.*

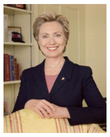
"I am a racially profiling doctor"
-- Satel, May 5, 2002, *New York Times*

"These [genetic] data also show that any two individuals within a particular population are as different genetically as any two people selected from any two populations in the world."
-- American Anthropological Association, 1997

Tabulation of DNA sequence differences among individuals

TTGCAGCTCTCC
TTGCAGCTCTCC

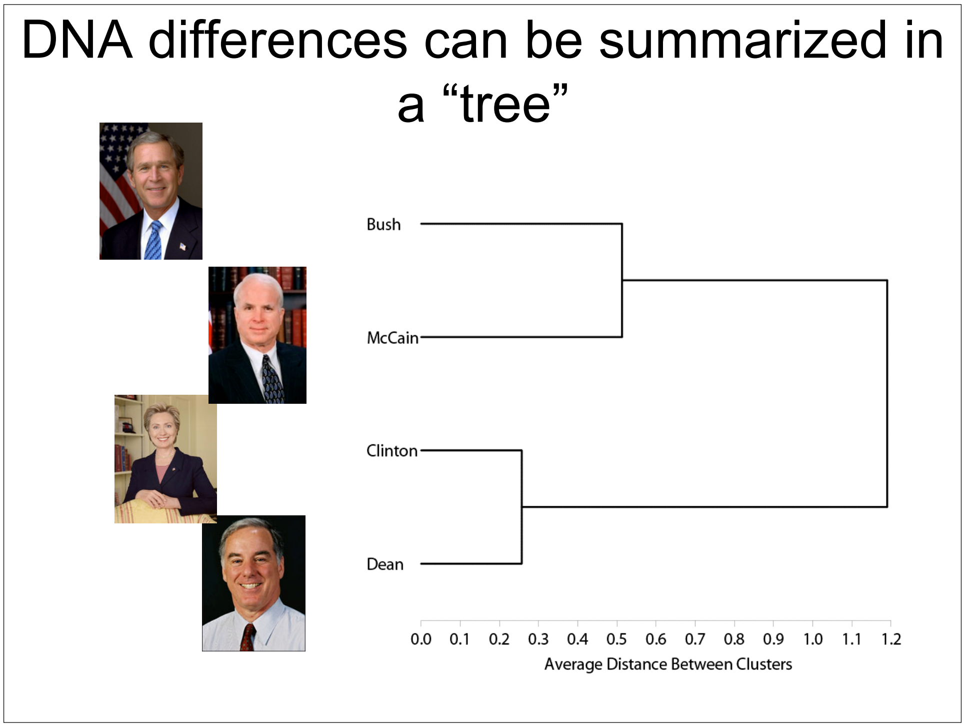
TTGCAGCTCTCC
$\boxed{A}$TGCAGCTCTC$\boxed{G}$



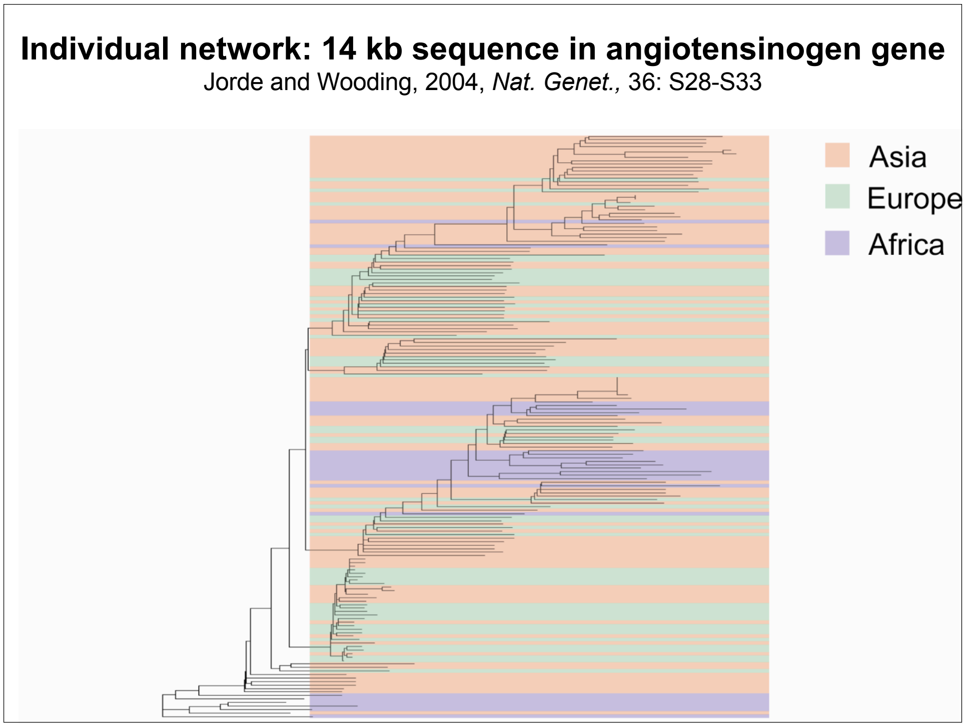
$\boxed{A}$TGCAGCTCTC$\boxed{G}$
$\boxed{A}$TGC$\boxed{T}$GCTCTC$\boxed{G}$

ATGCTGCTCTCG
ATGCTGCTCTCG

	Bush	McCain	Clinton	Dean
Bush	0	.	.	.
McCain	2	0	.	.
Clinton	5	3	0	.
Dean	6	4	1	0

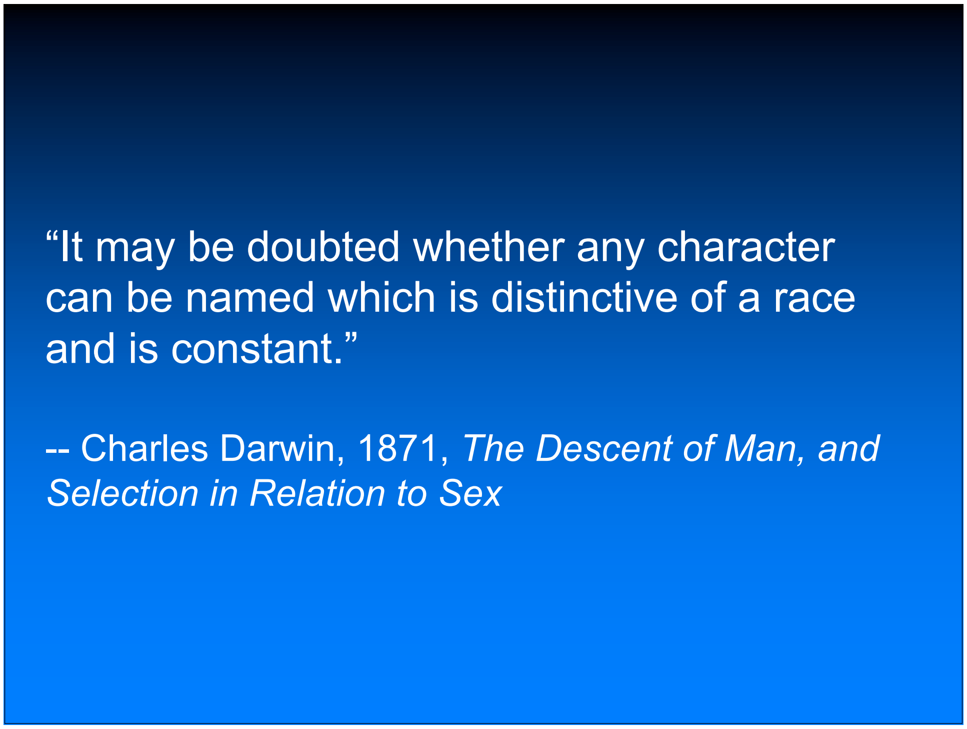


DNA differences can be summarized in a “tree”



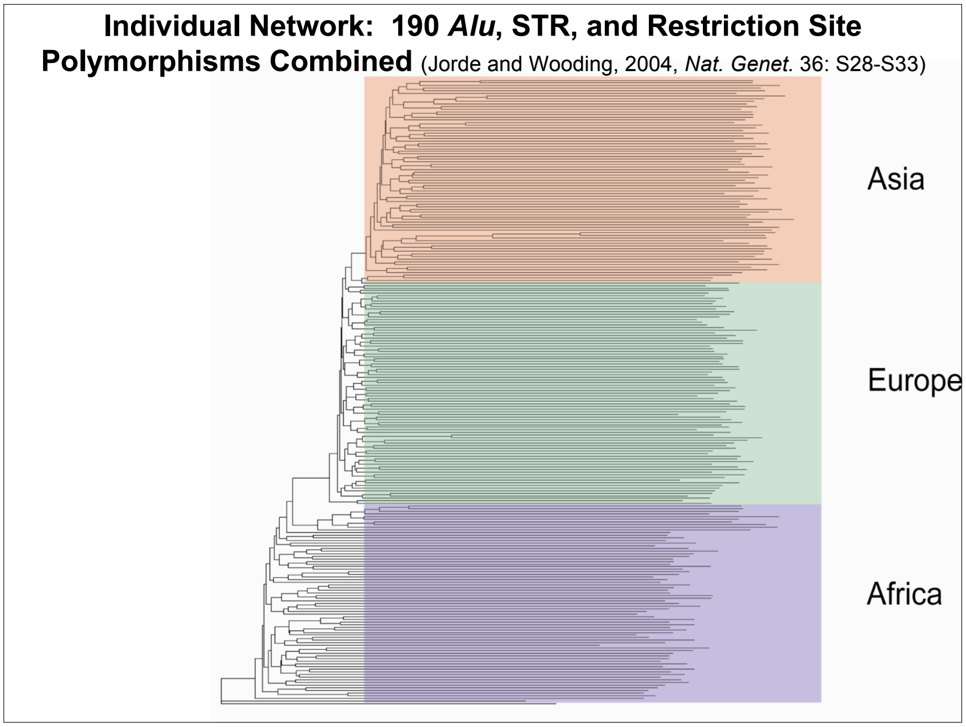
Individual network: 14 kb sequence in angiotensinogen gene

Jorde and Wooding, 2004, *Nat. Genet.,* 36: S28-S33

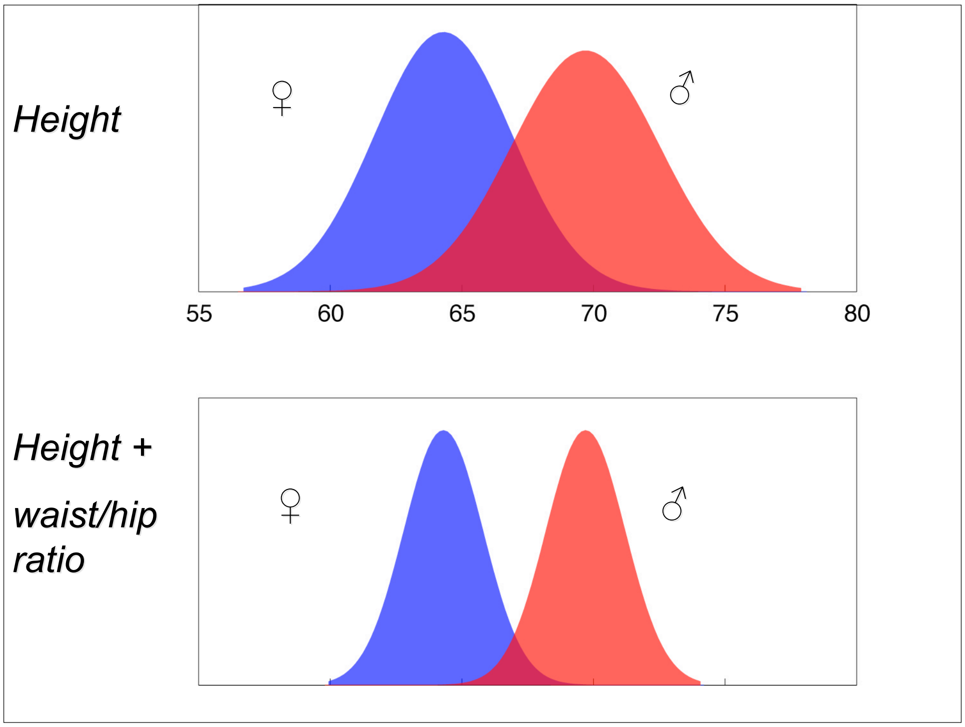


"It may be doubted whether any character can be named which is distinctive of a race and is constant."

-- Charles Darwin, 1871, *The Descent of Man, and Selection in Relation to Sex*



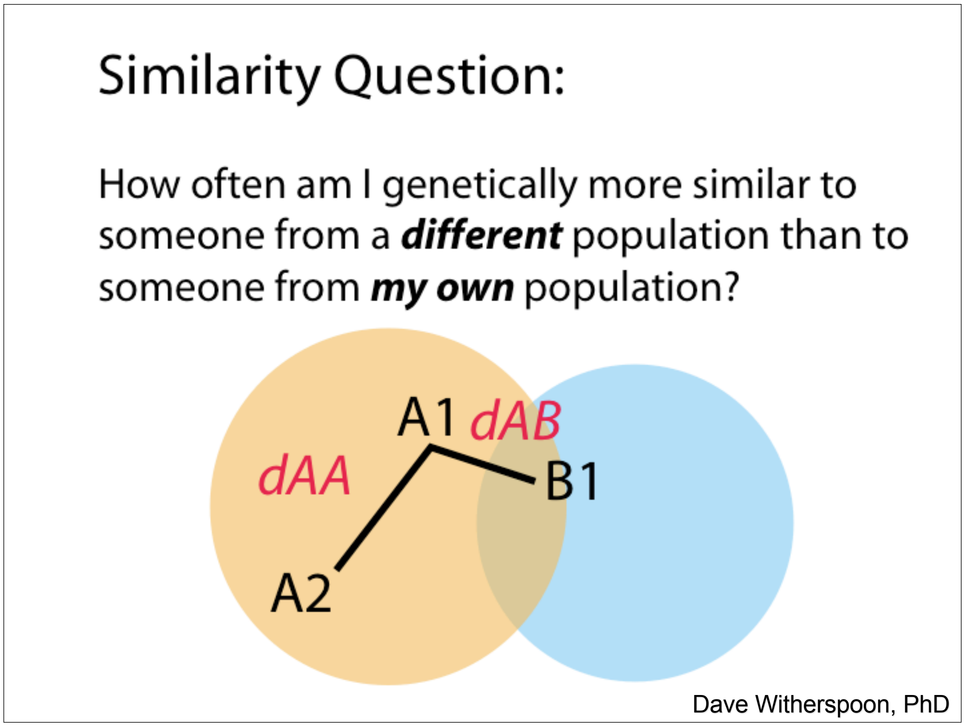
Individual Network: 190 *Alu*, STR, and Restriction Site Polymorphisms Combined (Jorde and Wooding, 2004, *Nat. Genet.* 36: S28-S33)



Height

Height +

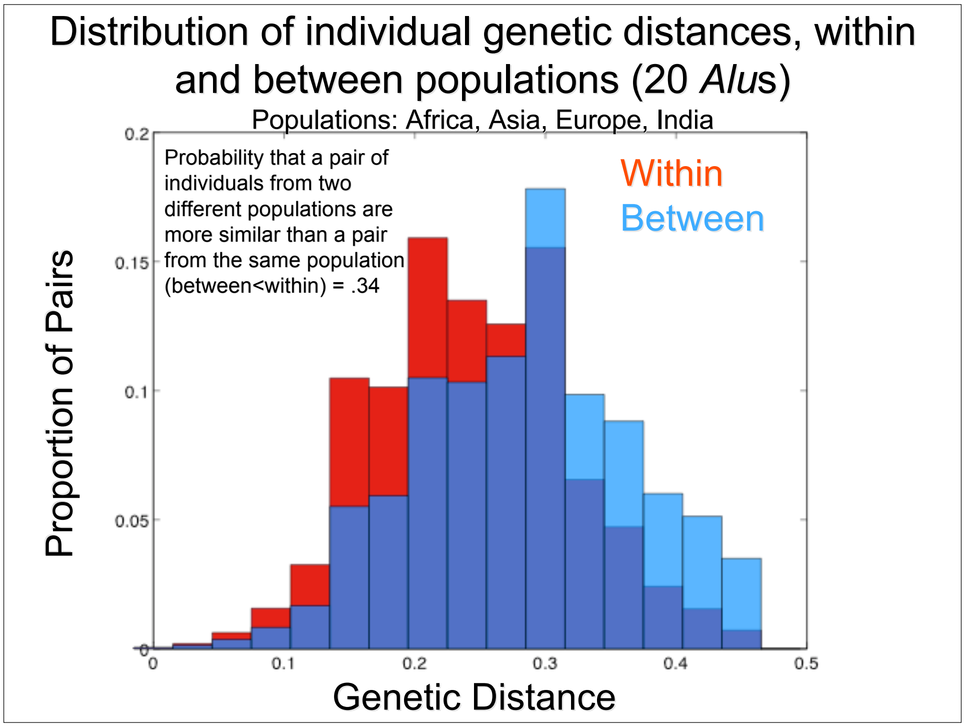
waist/hip ratio



Similarity Question:

How often am I genetically more similar to someone from a ***different*** population than to someone from ***my own*** population?

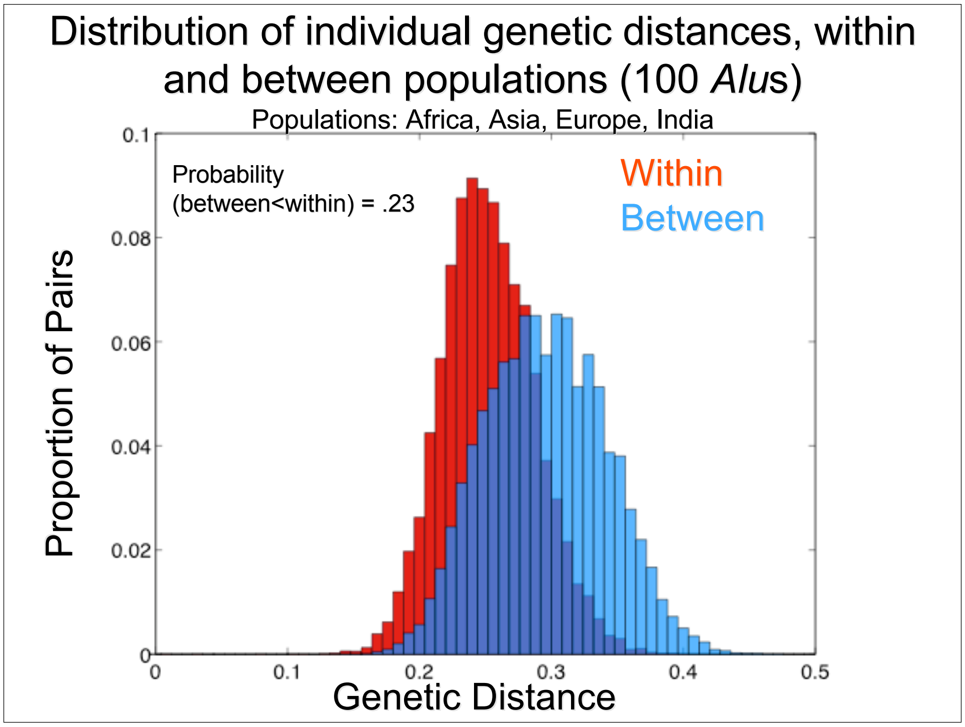
Dave Witherspoon, PhD



Distribution of individual genetic distances, within and between populations (20 *Alu*s)

Populations: Africa, Asia, Europe, India

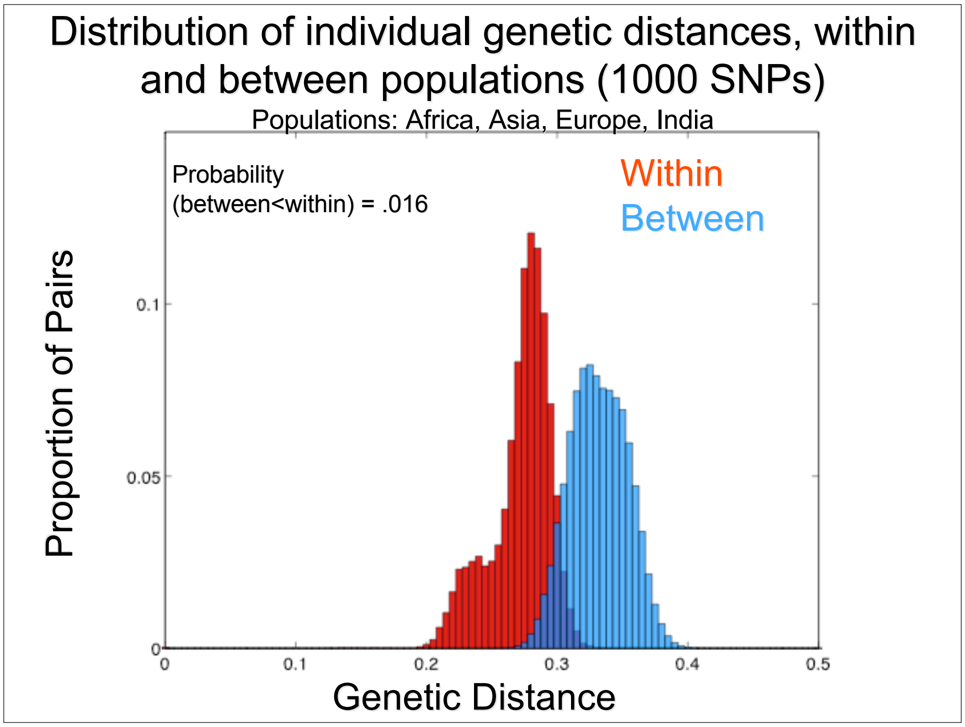
Probability that a pair of individuals from two different populations are more similar than a pair from the same population (between<within) = .34



Distribution of individual genetic distances, within and between populations (100 *Alu*s)

Populations: Africa, Asia, Europe, India

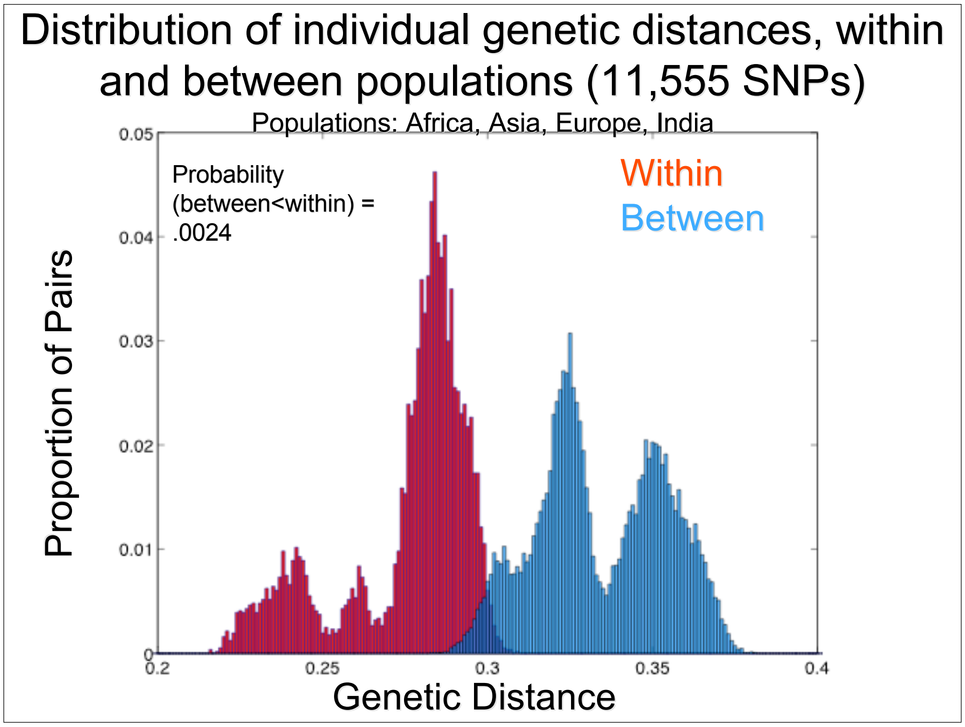
Probability (between<within) = .23



Distribution of individual genetic distances, within and between populations (1000 SNPs)

Populations: Africa, Asia, Europe, India

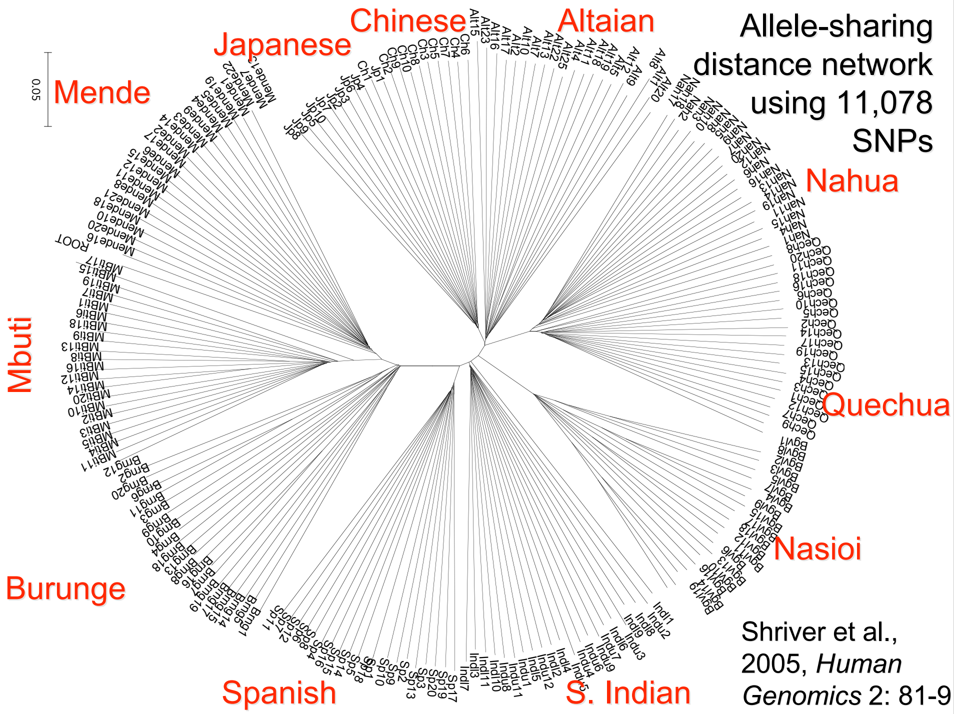
Probability (between<within) = .016



Distribution of individual genetic distances, within and between populations (11,555 SNPs)

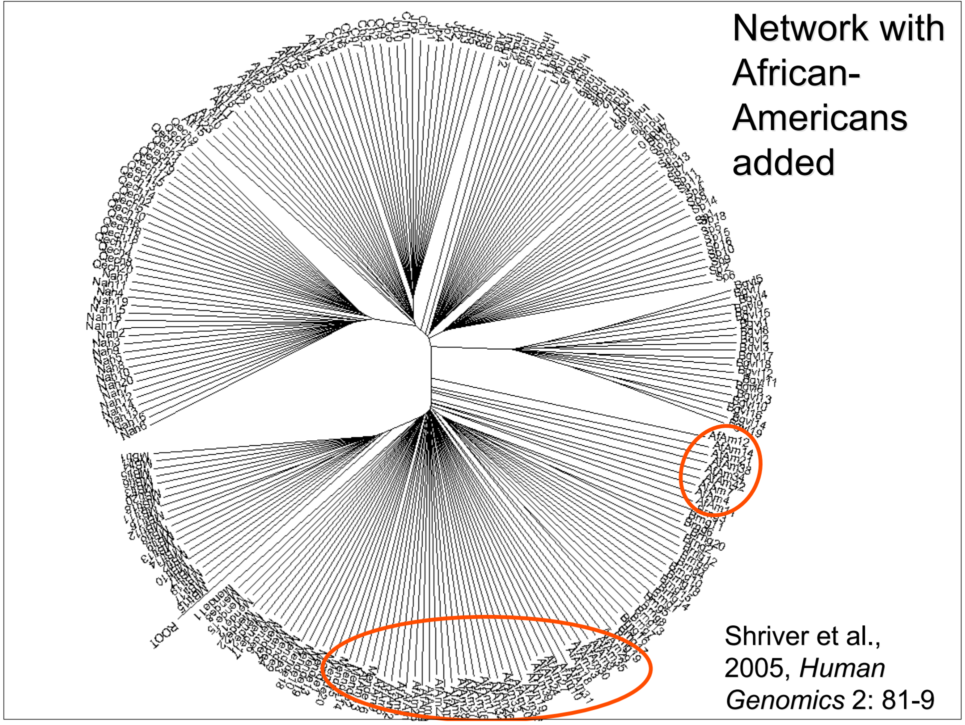
Populations: Africa, Asia, Europe, India

Probability (between<within) = .0024



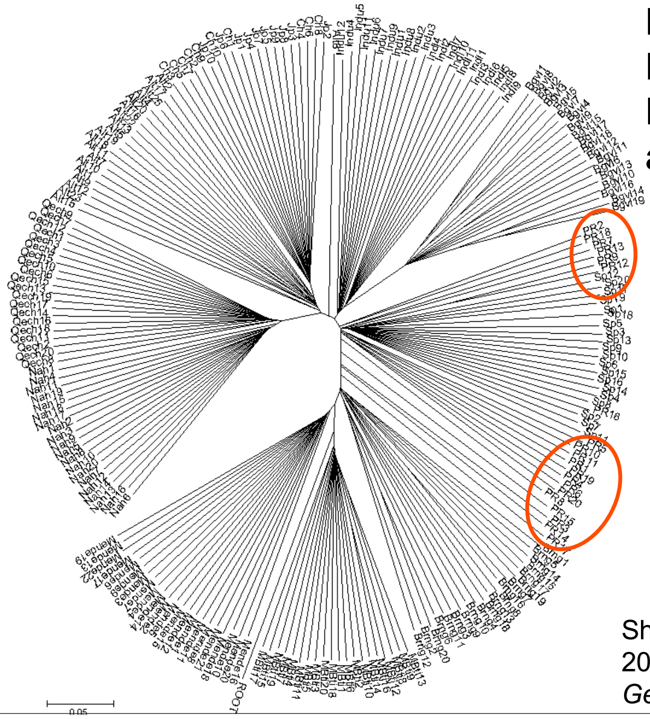
Allele-sharing distance network using 11,078 SNPs

Shriver et al., 2005, *Human Genomics* 2: 81-9



Network with African-Americans added

Shriver et al., 2005, *Human Genomics* 2: 81-9

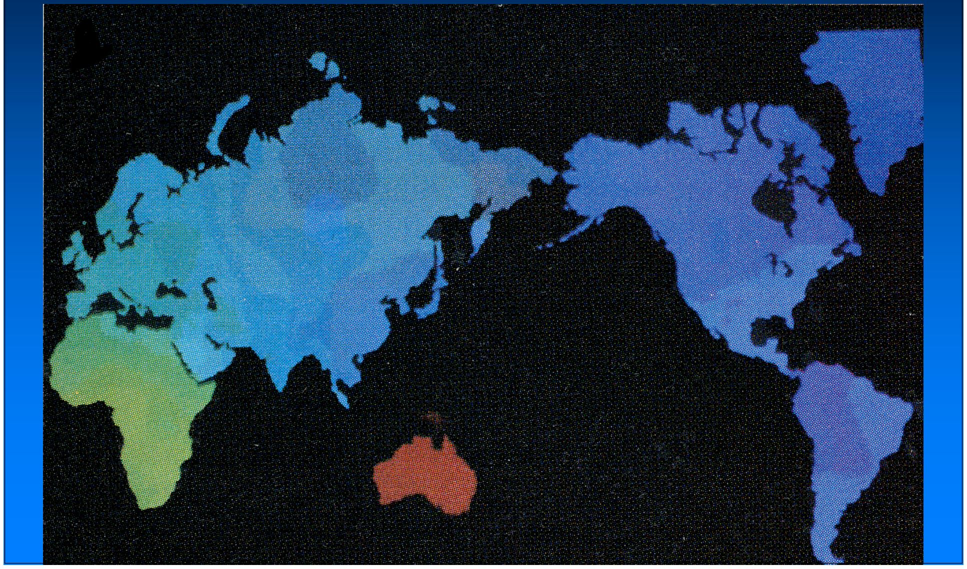


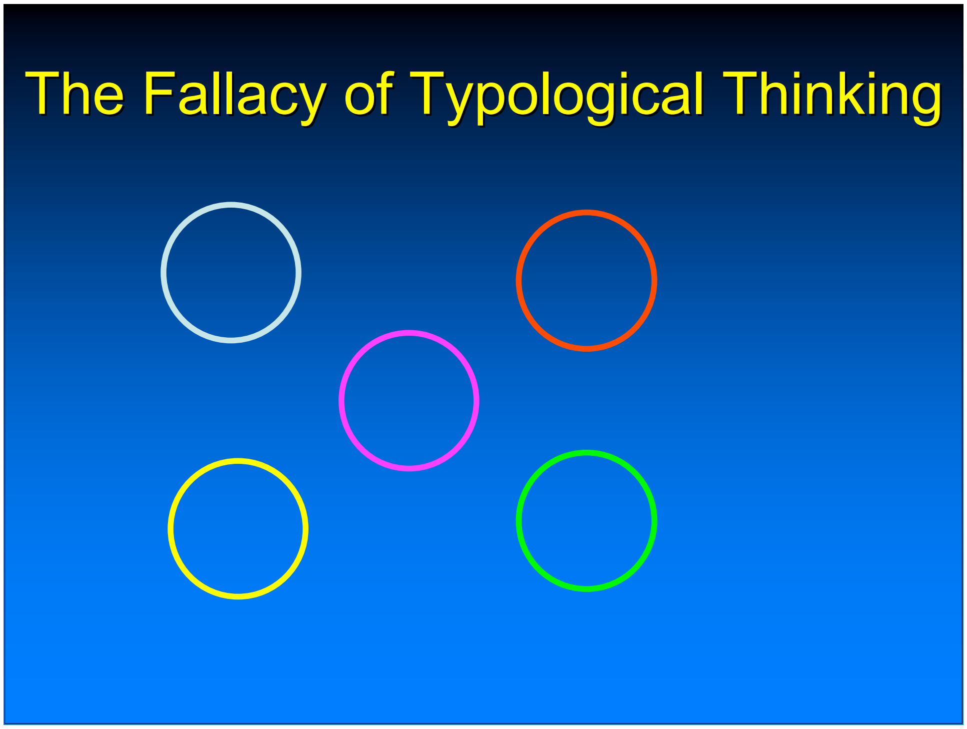
Network with Puerto Ricans added

Shriver et al., 2005, *Human Genomics* 2: 81-9

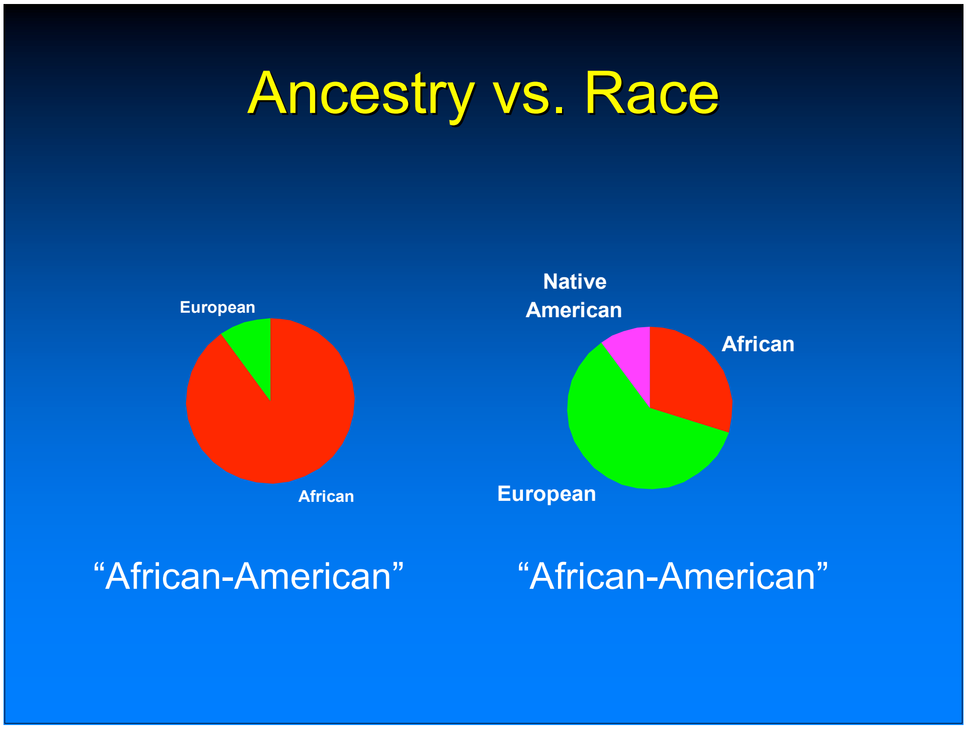
Worldwide Genetic Variation

Cavalli-Sforza et al., 1993, *Science*, 259: 639-46





The Fallacy of Typological Thinking



Ancestry vs. Race

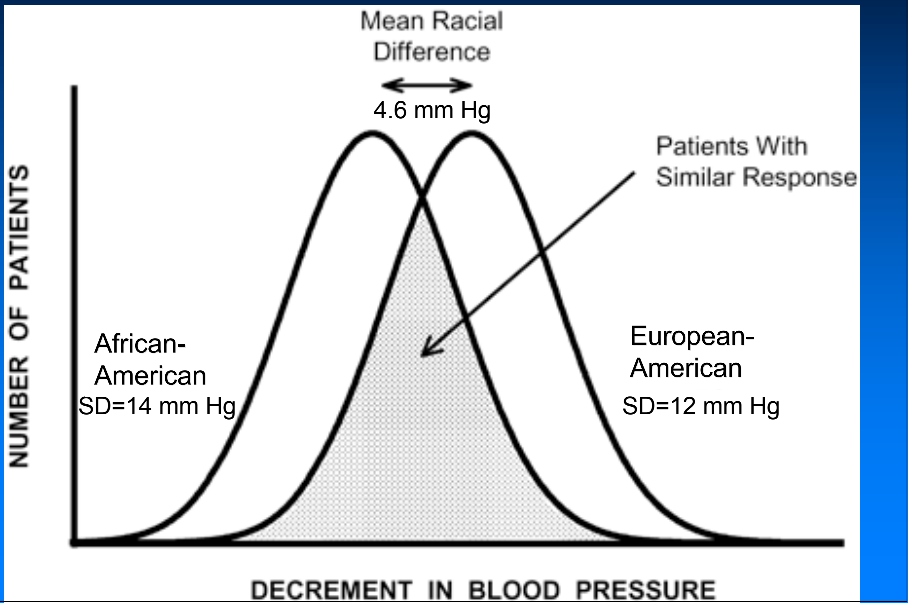
“African-American” “African-American”

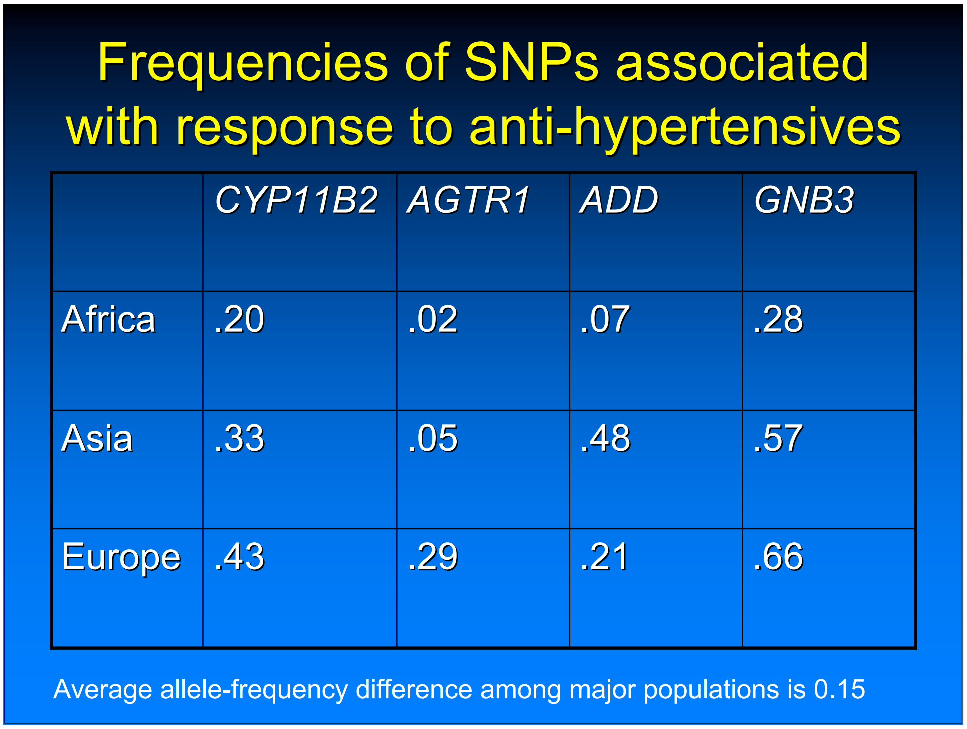
What do these findings imply for biomedicine?

- Large numbers of DNA polymorphisms can inform us about ancestry and population history
- Responses to many therapeutic drugs may involve variation in just a few genes (along with environmental variation)
- These variants typically differ between populations only in their *frequency* and imply substantial overlap between populations

Blood pressure response to ACE inhibitors

(Sehgal, 2004, *Hypertension* 43: 566-72)

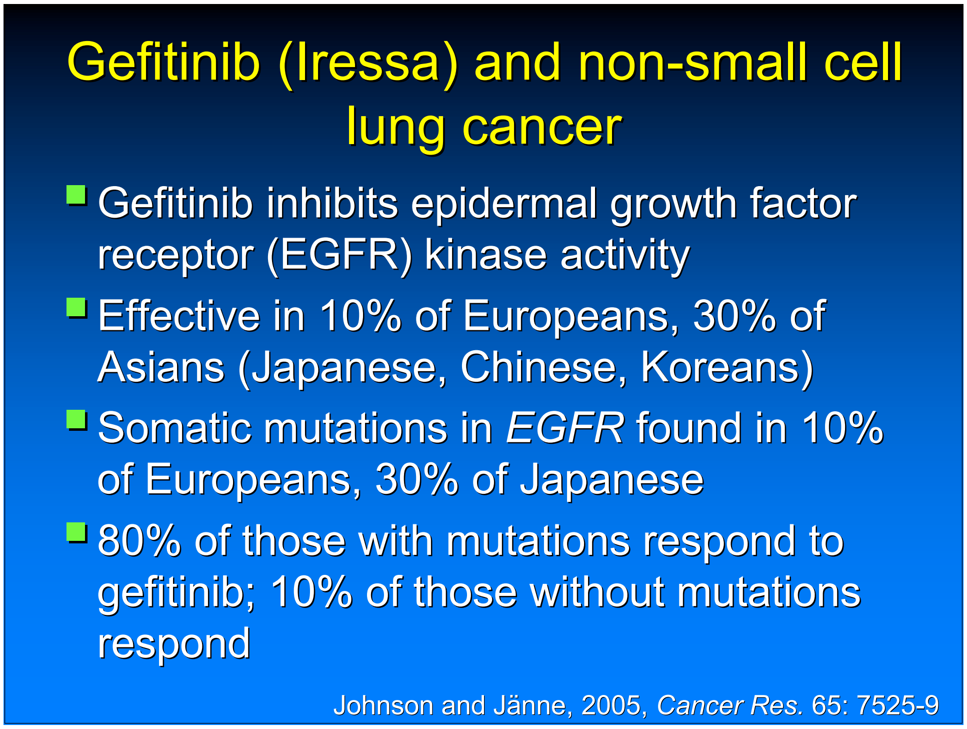




Frequencies of SNPs associated with response to anti-hypertensives

	CYP11B2	*AGTR1*	*ADD*	*GNB3*
Africa	.20	.02	.07	.28
Asia	.33	.05	.48	.57
Europe	.43	.29	.21	.66

Average allele-frequency difference among major populations is 0.15

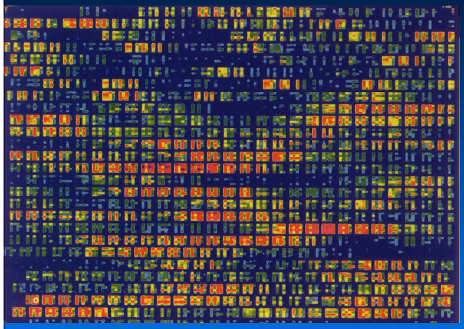


Gefitinib (Iressa) and non-small cell lung cancer

- Gefitinib inhibits epidermal growth factor receptor (EGFR) kinase activity
- Effective in 10% of Europeans, 30% of Asians (Japanese, Chinese, Koreans)
- Somatic mutations in *EGFR* found in 10% of Europeans, 30% of Japanese
- 80% of those with mutations respond to gefitinib; 10% of those without mutations respond

Johnson and Jänne, 2005, *Cancer Res.* 65: 7525-9

Microarrays and “personalized medicine”



Hundreds of thousands of different DNA sequences can be placed on a single array

These sequences are compared with DNA from a patient to test for mutations

Signals are rapidly processed by a computer

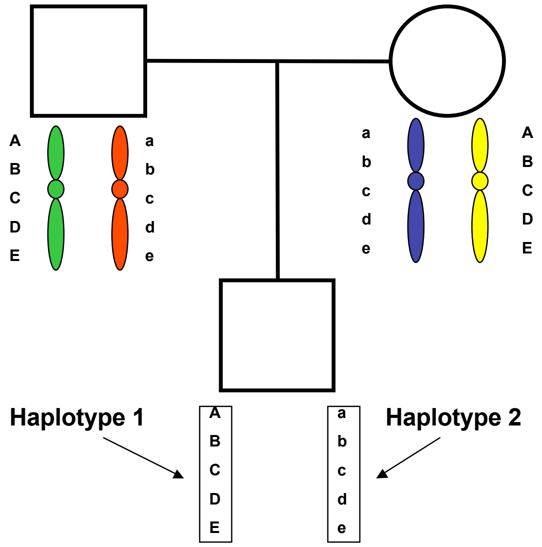
SNPs, haplotypes, linkage disequilibrium, and gene mapping

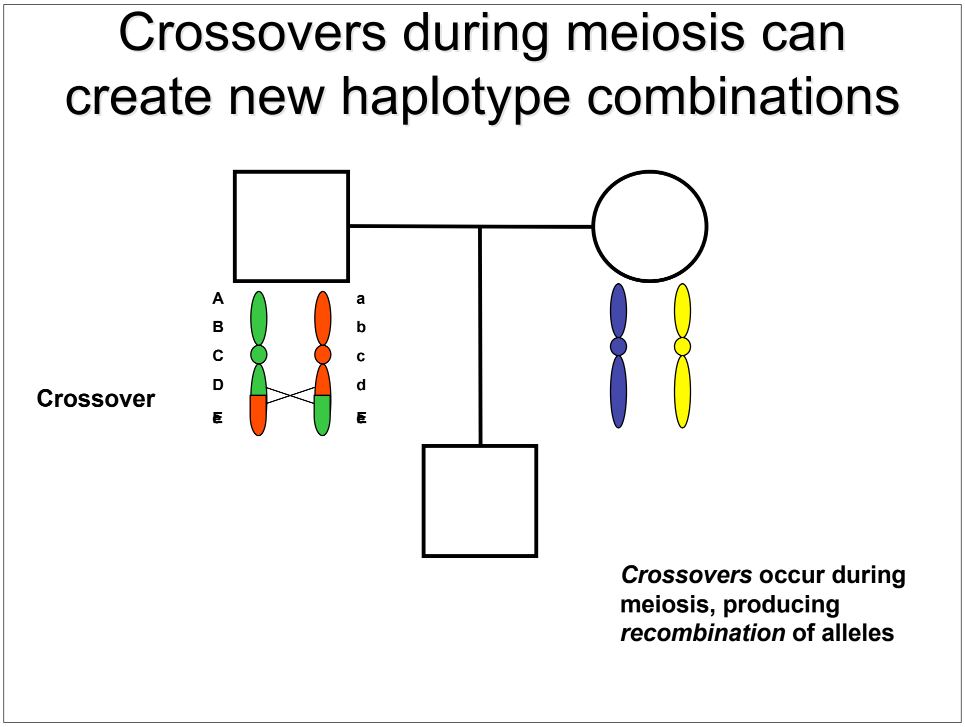
- A SNP with minor allele frequency (MAF) > 1% is found, on average, at 1/300 bp (roughly 10 million total)
- A “common” SNP (MAF > 5%) is found at about 1/600 bp (roughly 5 million total)
- SNPs have low mutation rates and can be typed by automated methods

Whole-genome association: the cost problem

- A whole-genome association study seeks any SNP allele that is found with elevated frequency in disease cases
- At $.001 per SNP, genotyping 5 million SNPs costs $5,000 per person
- A study involving 1,000 cases and 1,000 controls would cost $10,000,000
- Will SNP association reveal disease genes, and do we need to test all of these SNPs?

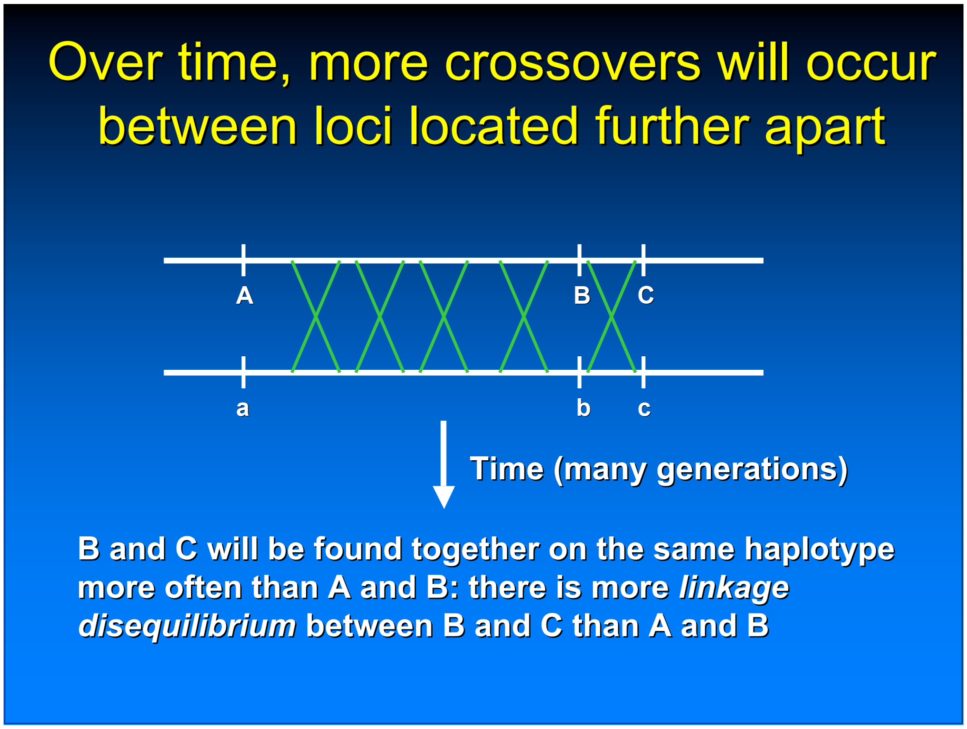
A *haplotype* is the DNA sequence found on one member of the chromosome pair





Crossovers during meiosis can create new haplotype combinations

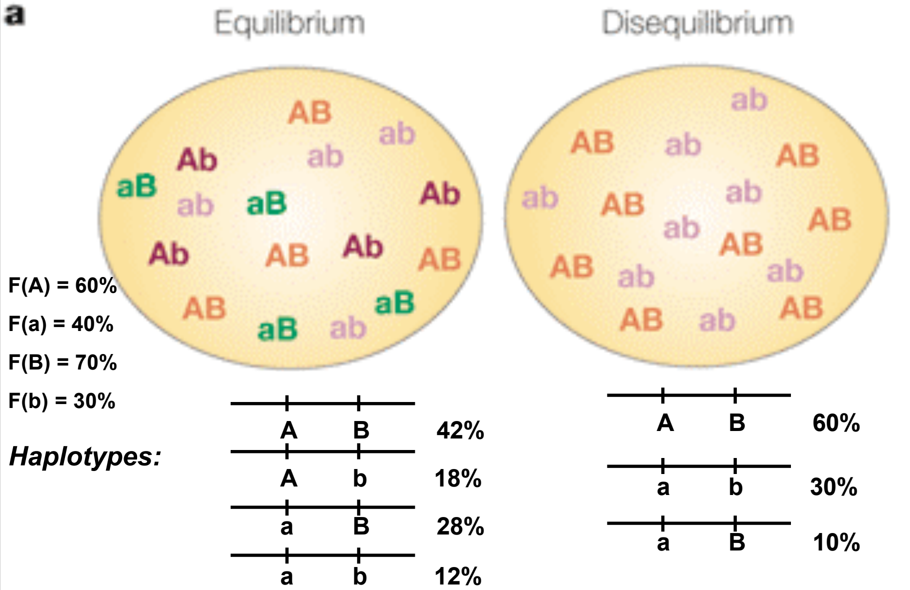
Crossovers occur during meiosis, producing *recombination* of alleles



Over time, more crossovers will occur between loci located further apart

B and C will be found together on the same haplotype more often than A and B: there is more *linkage disequilibrium* between B and C than A and B

Linkage disequilibrium: nonrandom association of alleles at linked loci



F(A) = 60%

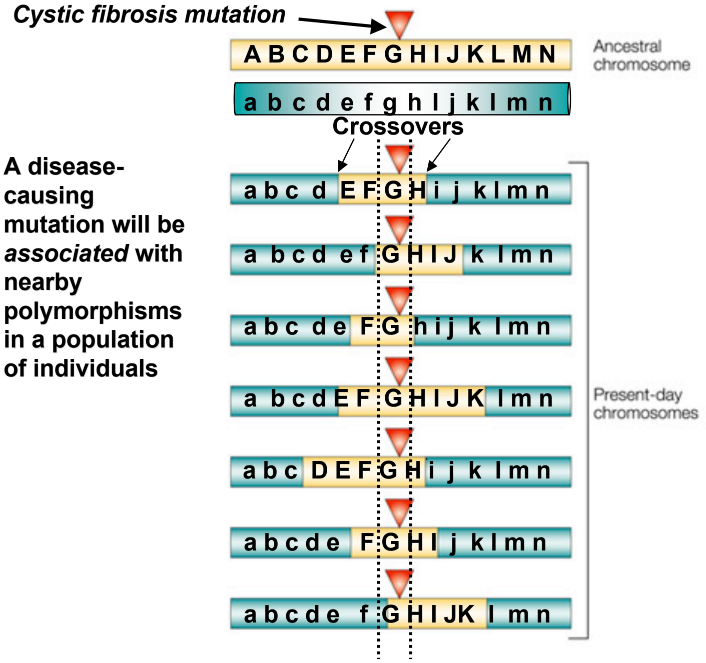
F(a) = 40%

F(B) = 70%

F(b) = 30%

Haplotypes:

Equilibrium		Disequilibrium	
A B	42%	A B	60%
A b	18%	a b	30%
a B	28%	a B	10%
a b	12%		

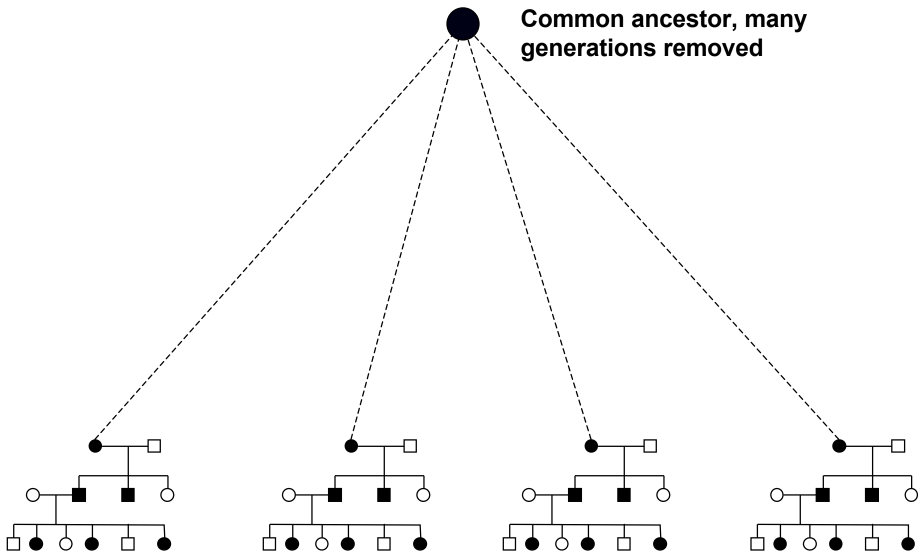

Cystic fibrosis mutation
A B C D E F G H I J K L M N
Ancestral chromosome
a b c d e f g h I j k l m n
Crossovers
a b c d E F G H i j k l m n
a b c d e f G H I J k l m n
a b c d e F G h i j k l m n
a b c d E F G H I J K l m n
a b c D E F G H i j k l m n
a b c d e F G H I j k l m n
a b c d e f G H I JK l m n
Present-day chromosomes

A disease-causing mutation will be *associated* with nearby polymorphisms in a population of individuals

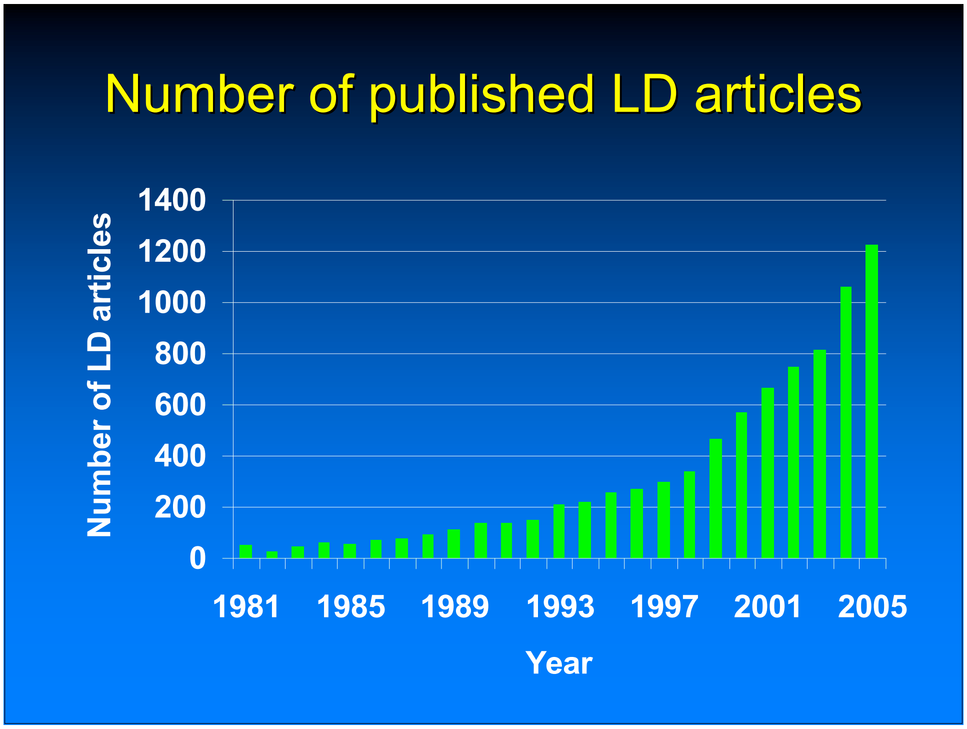
Potential advantages of linkage disequilibrium (LD)

- Family-based linkage studies of complex diseases often yield large candidate regions (~10-20 million base pairs)
- Association studies (linkage disequilibrium) can incorporate many past generations of recombination to narrow the candidate region
- Family data are *not* necessarily needed

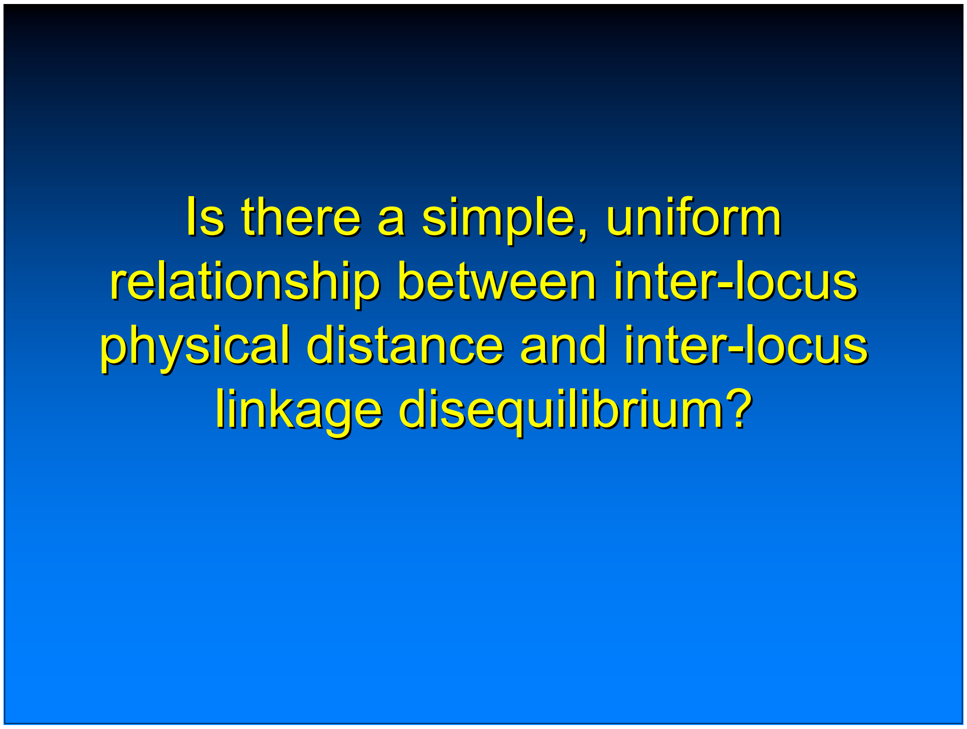
Populations are one big (complicated) pedigree



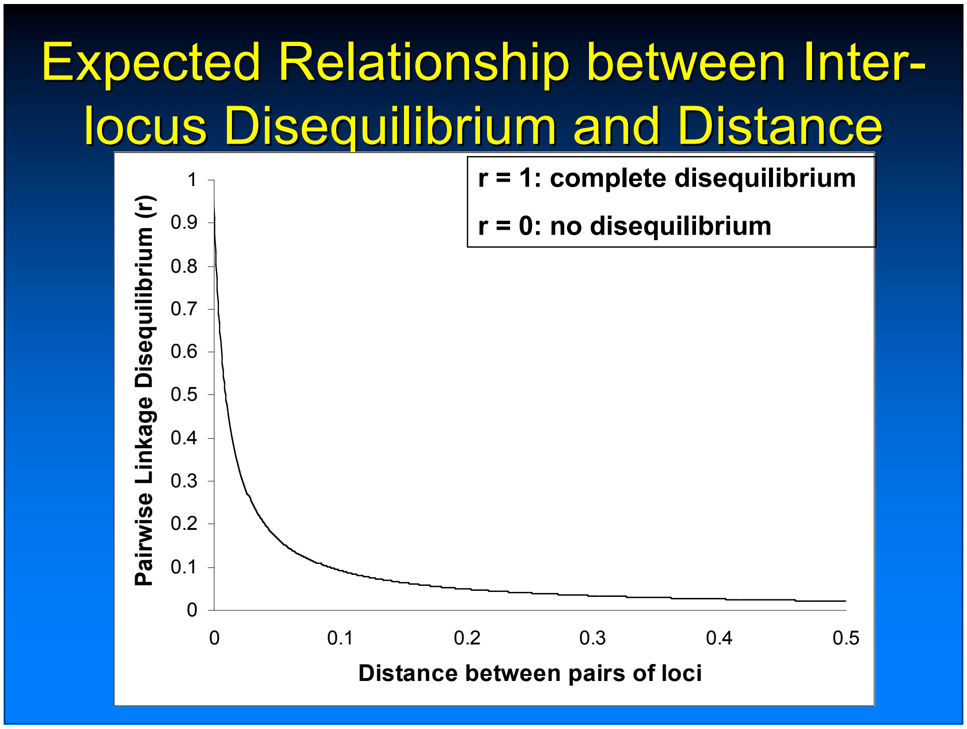
Common ancestor, many generations removed



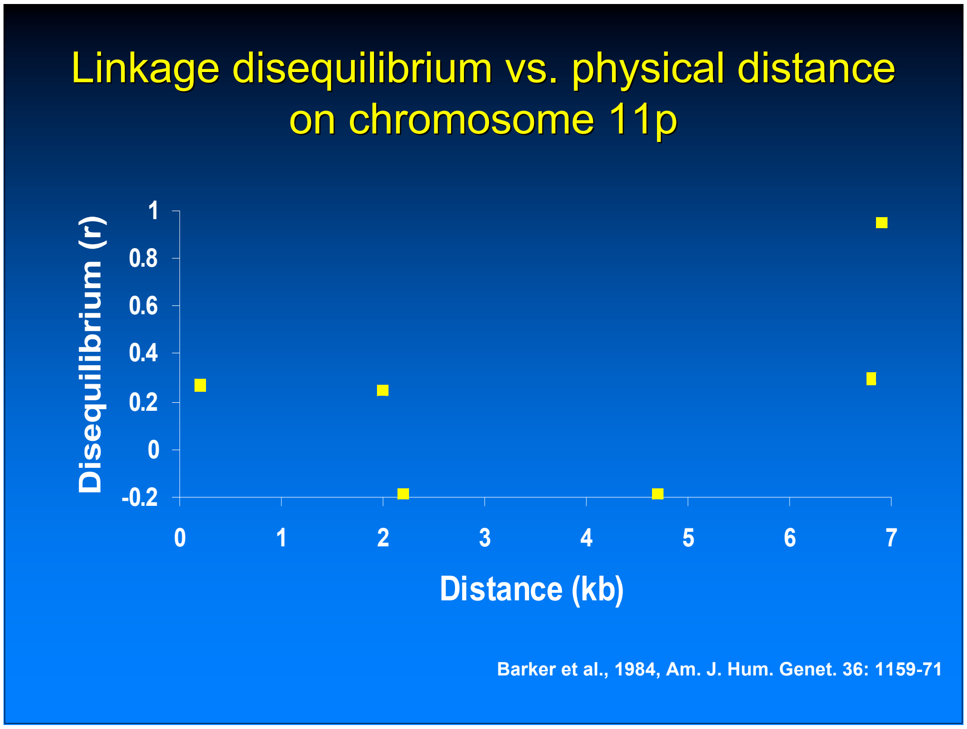
Number of published LD articles



Is there a simple, uniform relationship between inter-locus physical distance and inter-locus linkage disequilibrium?



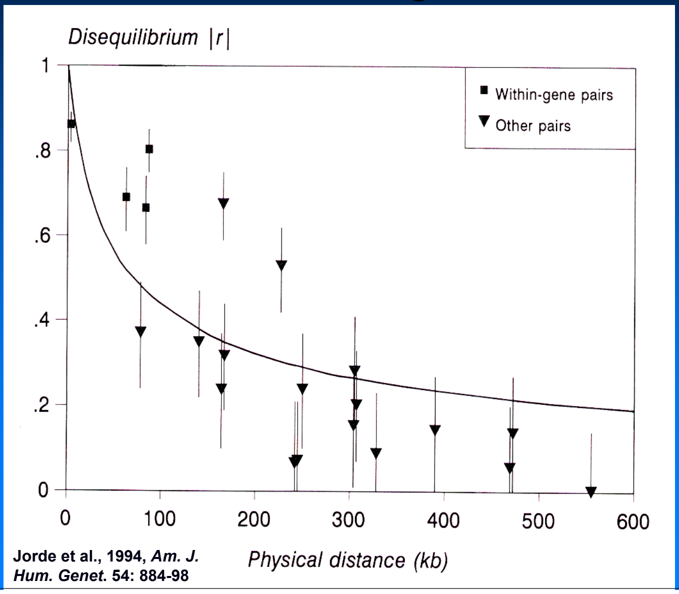
Expected Relationship between Inter-locus Disequilibrium and Distance



Linkage disequilibrium vs. physical distance on chromosome 11p

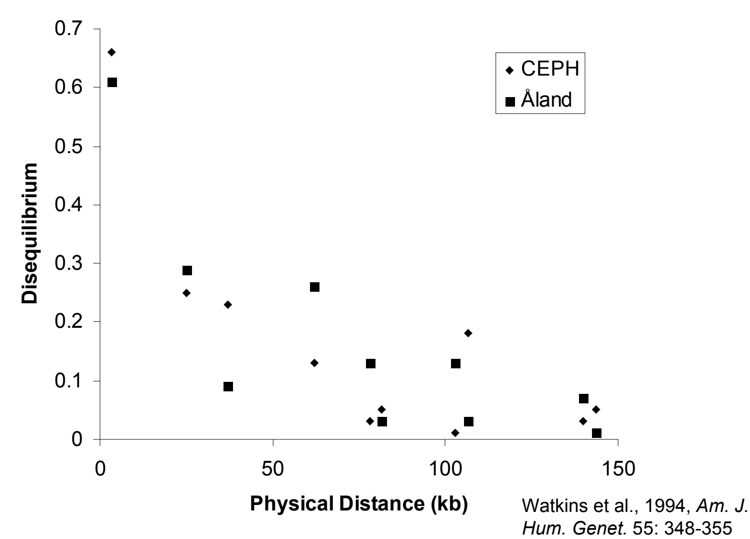
Barker et al., 1984, Am. J. Hum. Genet. 36: 1159-71

Disequilibrium between marker pairs in the *APC* region



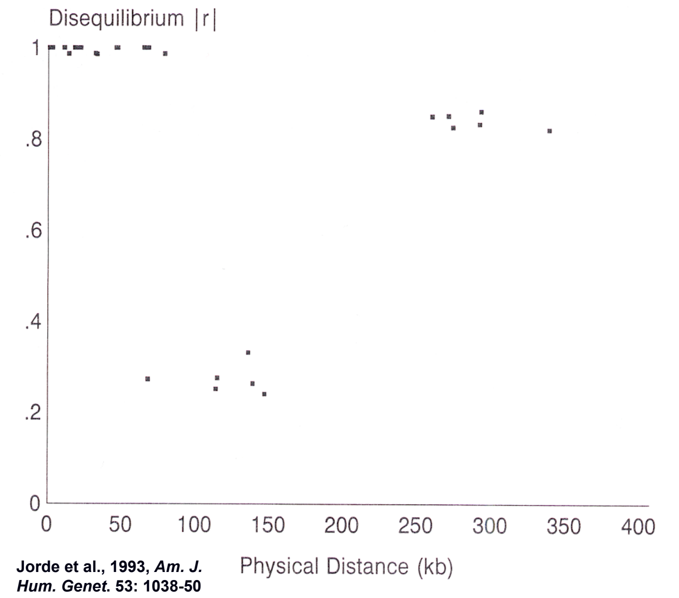
Jorde et al., 1994, *Am. J. Hum. Genet.* 54: 884-98

Linkage Disequilibrium and Physical Distance: *vWF* Region



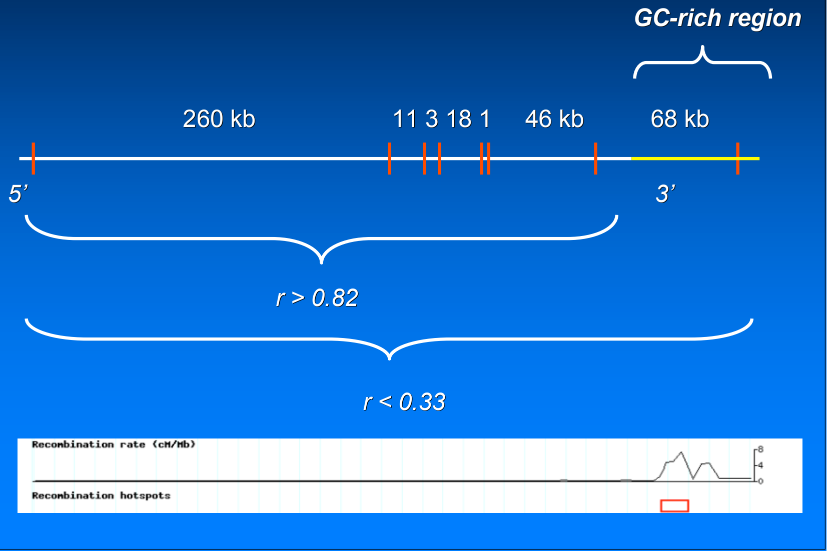
Watkins et al., 1994, *Am. J. Hum. Genet.* 55: 348-355

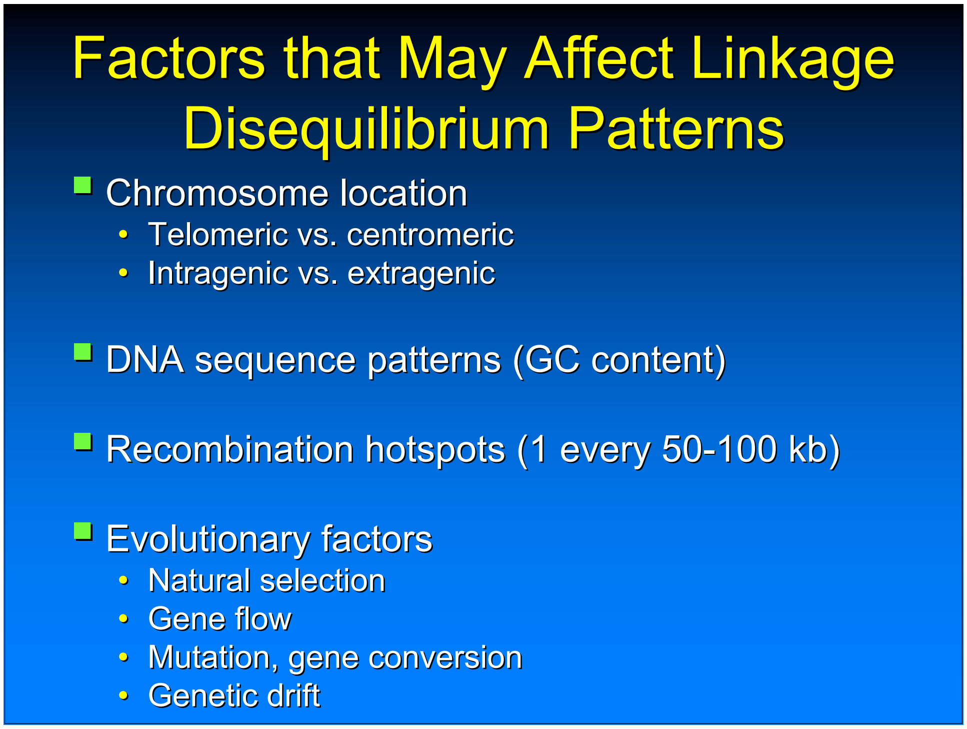
Disequilibrium in the *NF1* region



Jorde et al., 1993, *Am. J. Hum. Genet.* 53: 1038-50

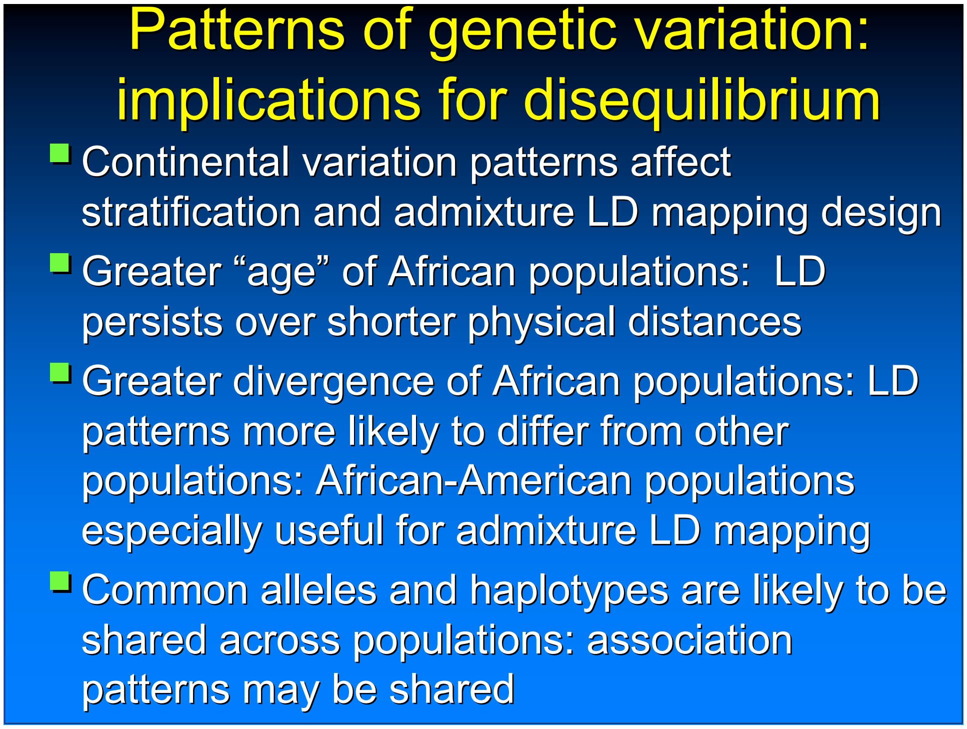
Uneven Disequilibrium Pattern in the NF1 Region





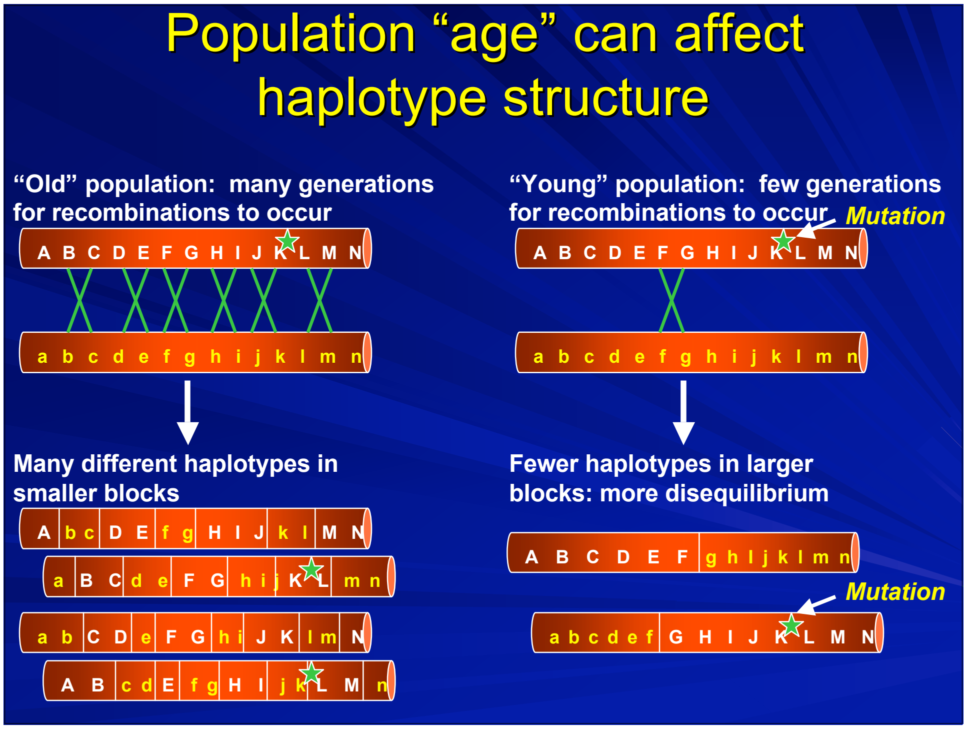
Factors that May Affect Linkage Disequilibrium Patterns

- Chromosome location
  - Telomeric vs. centromeric
  - Intragenic vs. extragenic
- DNA sequence patterns (GC content)
- Recombination hotspots (1 every 50-100 kb)
- Evolutionary factors
  - Natural selection
  - Gene flow
  - Mutation, gene conversion
  - Genetic drift



Patterns of genetic variation: implications for disequilibrium

- Continental variation patterns affect stratification and admixture LD mapping design
- Greater "age" of African populations: LD persists over shorter physical distances
- Greater divergence of African populations: LD patterns more likely to differ from other populations: African-American populations especially useful for admixture LD mapping
- Common alleles and haplotypes are likely to be shared across populations: association patterns may be shared



Population “age” can affect haplotype structure

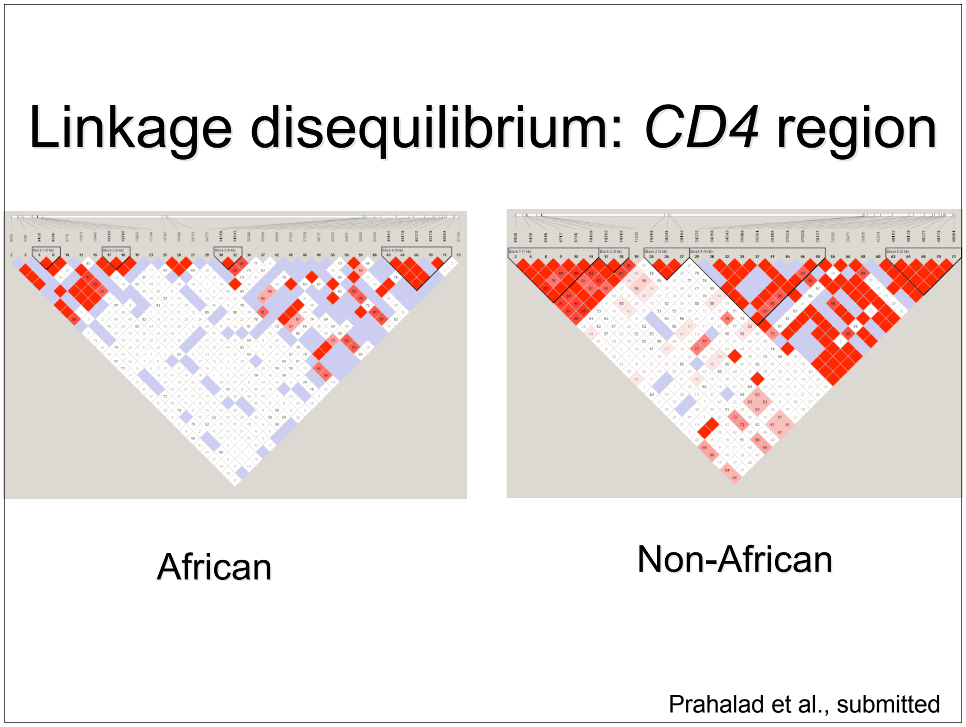
“Old” population: many generations for recombinations to occur

“Young” population: few generations for recombinations to occur

Many different haplotypes in smaller blocks

Fewer haplotypes in larger blocks: more disequilibrium

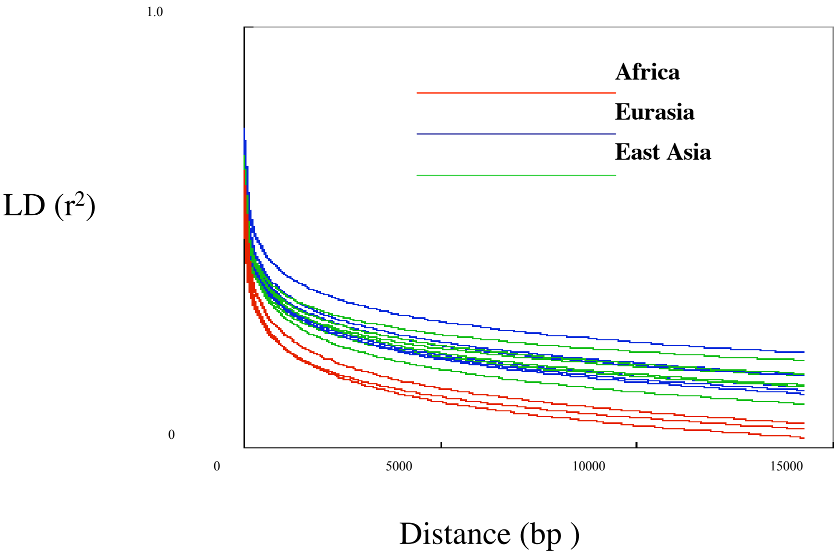
Mutation
A B C D E F G H I J K L M N
a b c d e f g h i j k l m n
A B C D E F G H I J K L M N
a b c d e f g h i j k l m n
A b c D E f g H I J k l M N
a B C d e F G h i j K L m n
a b C D e F G h i J K l m N
A B c d E f g H I j k L M n
A B C D E F g h i j k l m n
Mutation
a b c d e f G H I J K L M N



Linkage disequilibrium: *CD4* region

Prahalad et al., submitted

Population variation in *AGT* disequilibrium



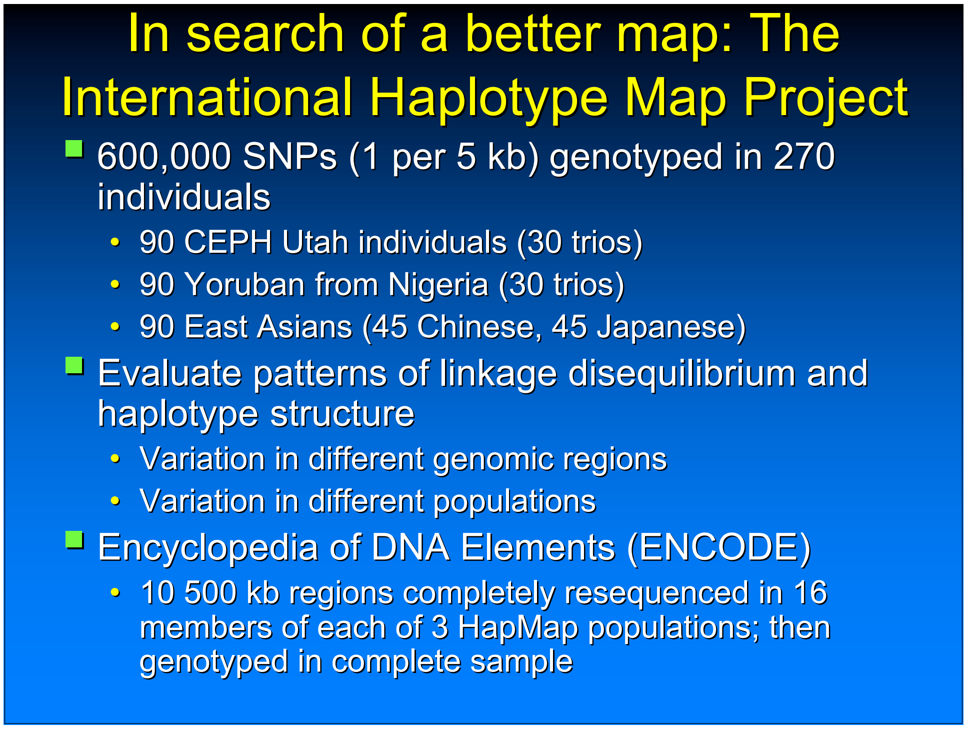
Nakajima et al., 2004, *Am. J. Hum. Genet.* 74: 898-

How general are these patterns?

To what extent does LD vary with genomic location and population?

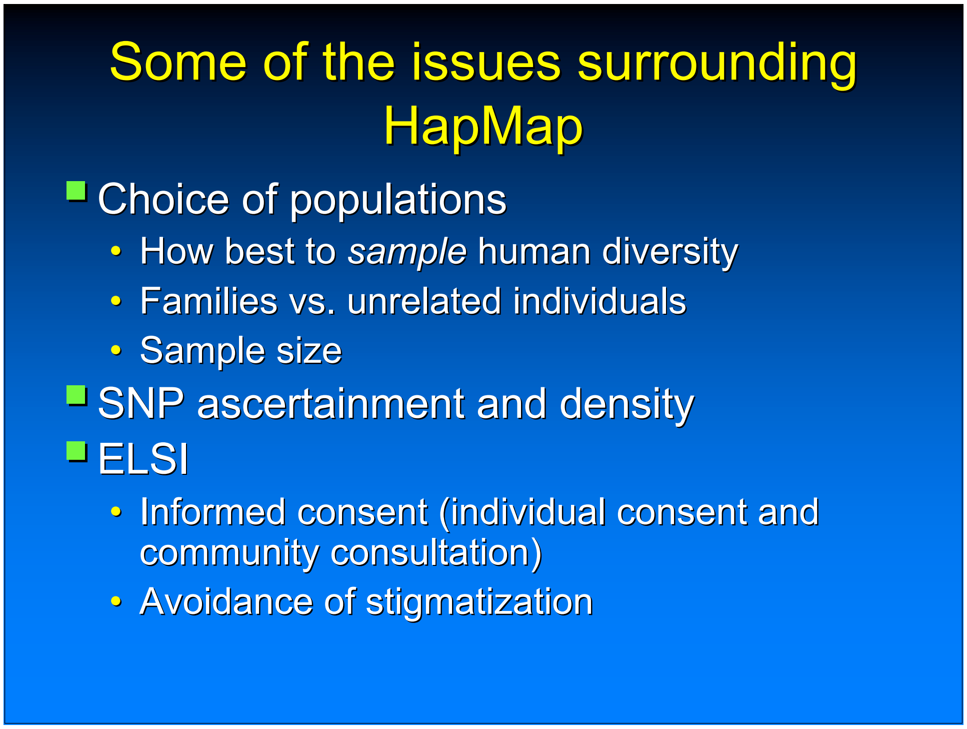
A Map of the World, 1544

CHARTA COSMOGRAPHICA, CVM VENTORVM PROPRIA NATVRA ET OPERATIONE.
Circius, Noordt noordtweſt. SEPTEN Septentrionalis, Noordt. TRIO Aquilo, Noordt noordt ooſt.
OCCI Zephyrus DENS. Weſt.
ORI Subſolanus ENS. Ooſt.
Zona frigida
ASIA
AFRICA
AMERICA
PERV
Aequinoctialis
Oceanus Indicus Meridianalis
REGIONVM LONGITVDO AD ORTVM.
Auſtroafricus, Zuydt zuydtweſt. MERI Auſter, Zuydt DIES. Euroaſter, Zuydt zuydtooſt.



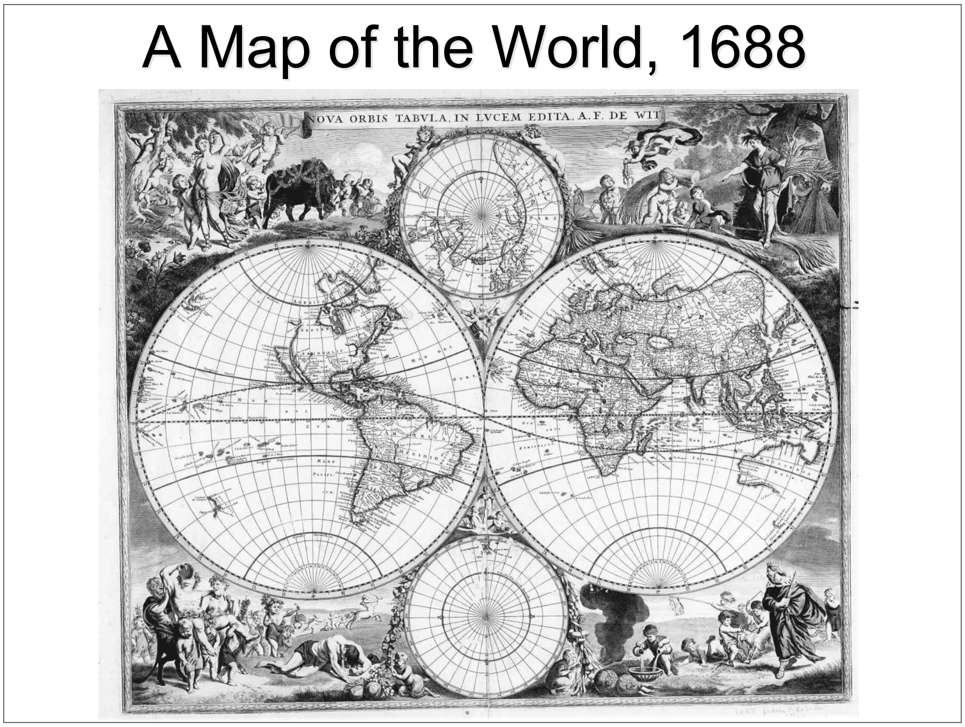
In search of a better map: The International Haplotype Map Project

- 600,000 SNPs (1 per 5 kb) genotyped in 270 individuals
  - 90 CEPH Utah individuals (30 trios)
  - 90 Yoruban from Nigeria (30 trios)
  - 90 East Asians (45 Chinese, 45 Japanese)
- Evaluate patterns of linkage disequilibrium and haplotype structure
  - Variation in different genomic regions
  - Variation in different populations
- Encyclopedia of DNA Elements (ENCODE)
  - 10 500 kb regions completely resequenced in 16 members of each of 3 HapMap populations; then genotyped in complete sample

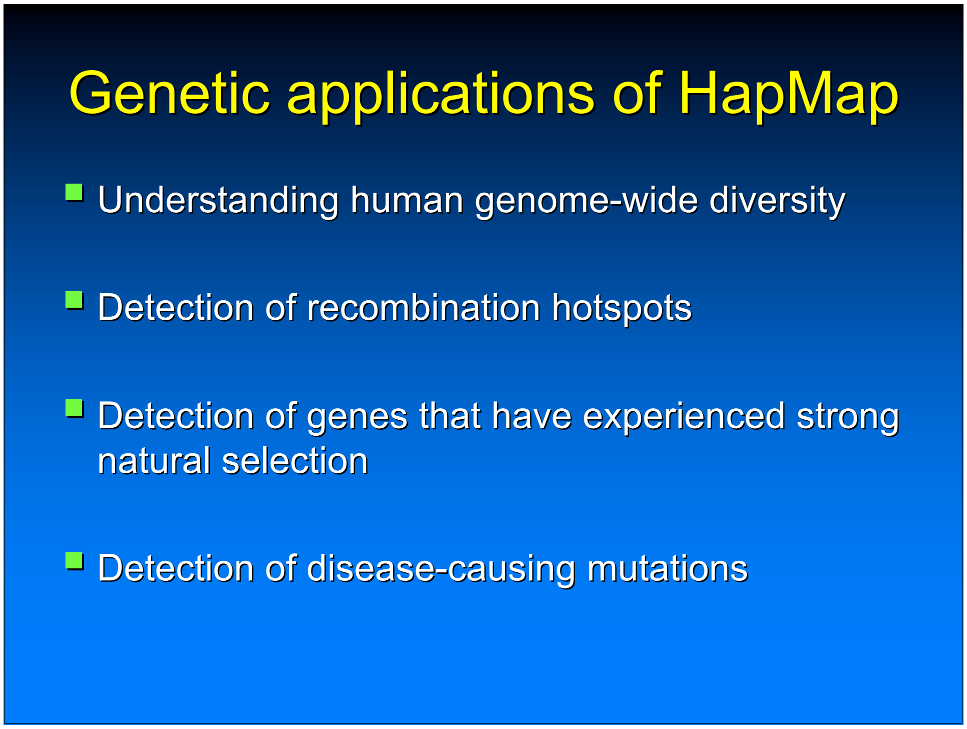


Some of the issues surrounding HapMap

- Choice of populations
  - How best to *sample* human diversity
  - Families vs. unrelated individuals
  - Sample size
- SNP ascertainment and density
- ELSI
  - Informed consent (individual consent and community consultation)
  - Avoidance of stigmatization



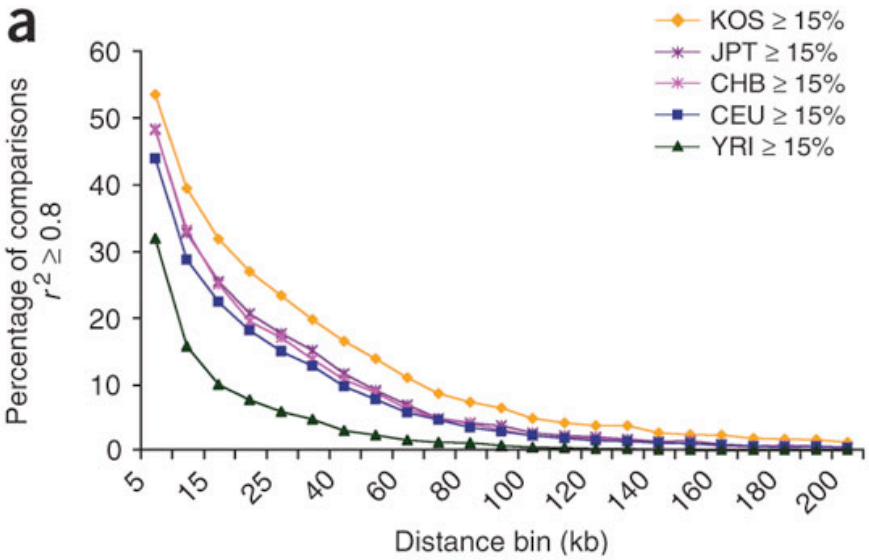
A Map of the World, 1688



Genetic applications of HapMap

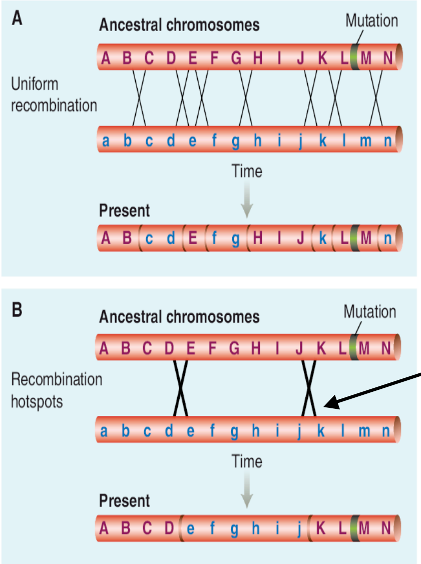
- Understanding human genome-wide diversity
- Detection of recombination hotspots
- Detection of genes that have experienced strong natural selection
- Detection of disease-causing mutations

LD decline in Kosrae, an isolate, compared to HapMap samples



Bonnen et al., 2006, *Nat. Genet.* 38: 214-7

Recombination hotspots and haplotype blocks

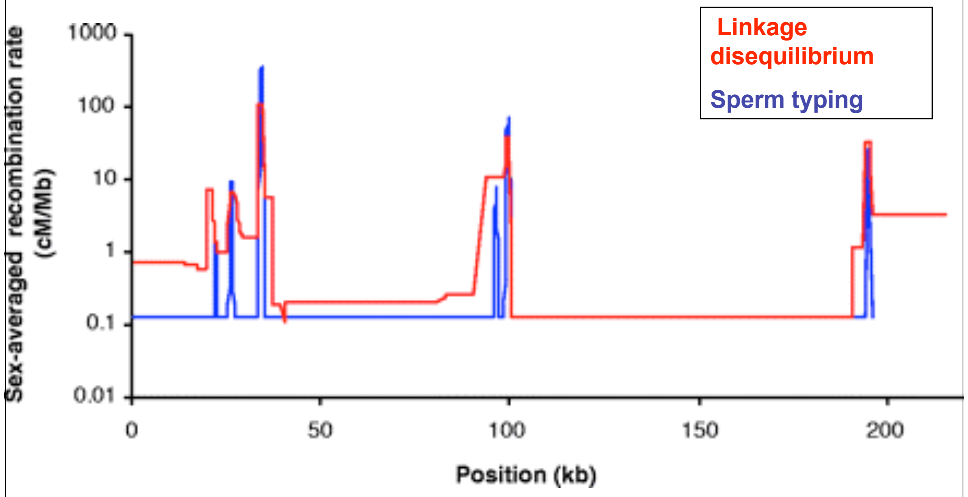

A
Ancestral chromosomes
Mutation
A B C D E F G H I J K L M N
Uniform recombination
a b c d e f g h i j k l m n
Time
Present
A B c d E f g H I J k L M n
B
Ancestral chromosomes
Mutation
A B C D E F G H I J K L M N
Recombination hotspots
a b c d e f g h i j k l m n
Time
Present
A B C D e f g h i j K L M N

Recombination elevated at least 10X in a 1-2 kb region

Recombination hotspots

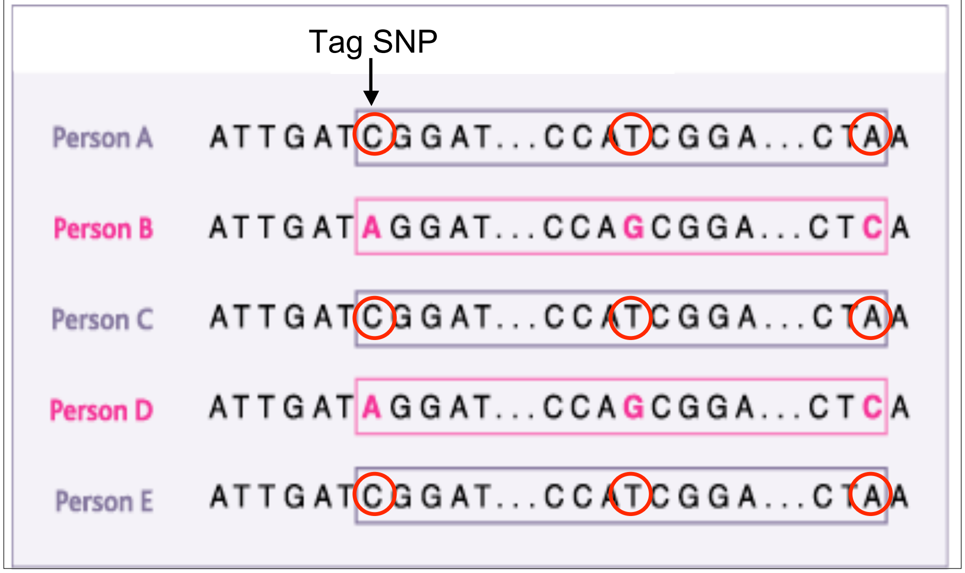
- LD patterns indicate 25,000 - 50,000 hotspots in human genome (1 every 50 – 100 kb) (Myers et al., 2005, *Science* 310: 321-4)
- 80% of recombination occurs in ~15% of the genome
- Hotspots are not congruent in human and chimpanzee, despite 99% sequence identity: suggests hotspots evolve rapidly and may not be sequence-dependent

Linkage disequilibrium detects true recombination hotspots accurately



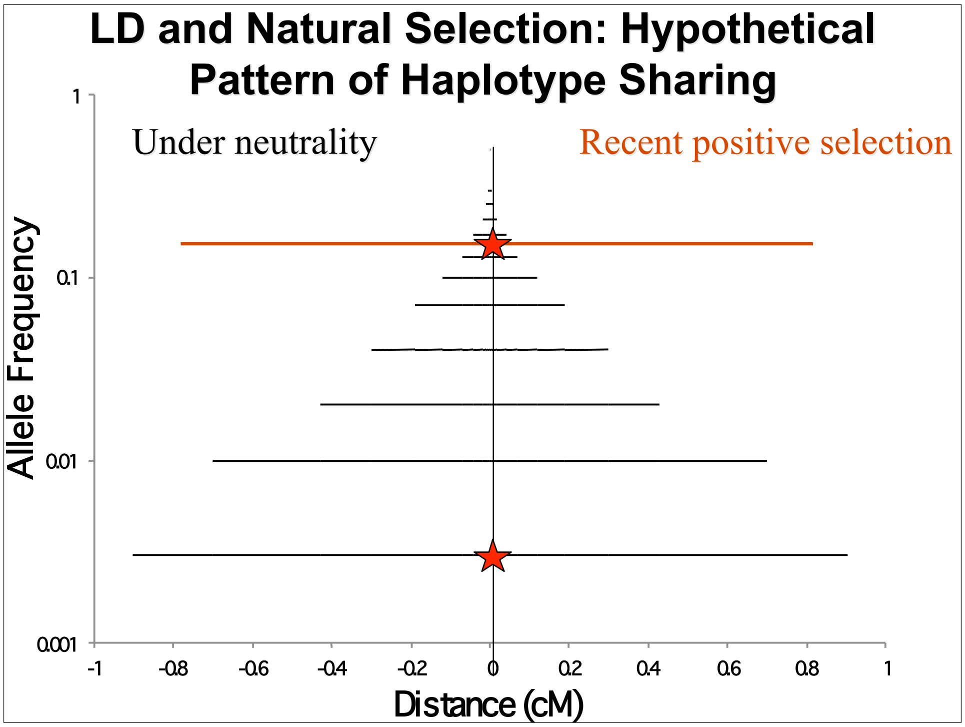
McVean et al., 2004, *Science* 304: 581-4

SNPs in disequilibrium are redundant: we don't need to type all of them

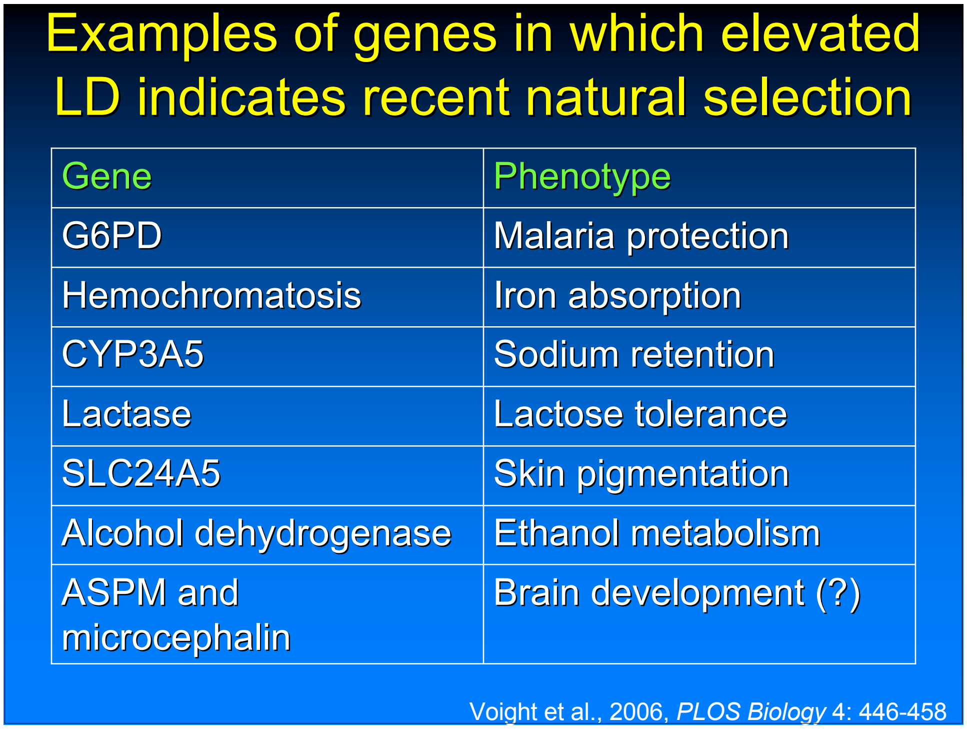

Tag SNP
Person A ATTGATCGGAT...CCATCGGA...CTAA
Person B ATTGATAGGAT...CCAGCGGA...CTCA
Person C ATTGATCGGAT...CCATCGGA...CTAA
Person D ATTGATAGGAT...CCAGCGGA...CTCA
Person E ATTGATCGGAT...CCATCGGA...CTAA

Portability of HapMap patterns to other populations

HapMap population	Comparative population	Reference
Asian	Chinese, Japanese, Korean	Lim, 2006, Genomics
European	Australian	Stankovich, 2006, Hum. Genet.
European	Finnish	Willer, 2006, Genet. Epidemiol.
European	Estonian	Montpetit, 2006, PLOS Genetics
European	Spanish	Ribas, 2006, Hum. Genet.
European	Other European	Mueller, 2005, AJHG



LD and Natural Selection: Hypothetical Pattern of Haplotype Sharing



Examples of genes in which elevated LD indicates recent natural selection

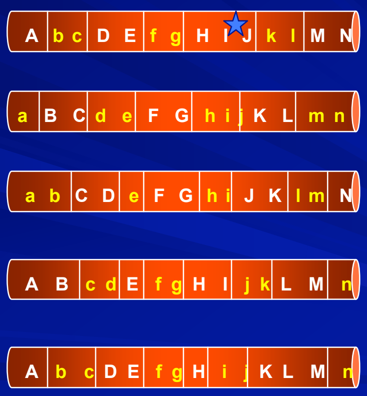
Gene	Phenotype
G6PD	Malaria protection
Hemochromatosis	Iron absorption
CYP3A5	Sodium retention
Lactase	Lactose tolerance
SLC24A5	Skin pigmentation
Alcohol dehydrogenase	Ethanol metabolism
ASPM and microcephalin	Brain development (?)

Voight et al., 2006, *PLOS Biology* 4: 446-458

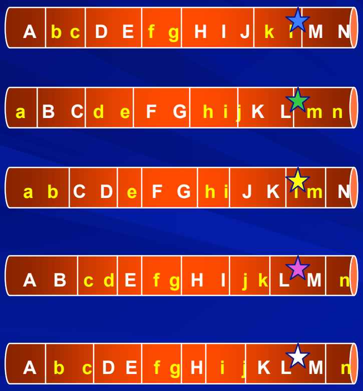
Linkage disequilibrium and single-gene diseases: many successes

- Cystic fibrosis
- Hemochromatosis
- Wilson disease
- Friedreich’s ataxia
- Bloom syndrome
- Werner syndrome
- Progressive myoclonus epilepsy
- Torsion dystonia
- Diastrophic dysplasia (and many other “Finnish” diseases)

Association (linkage disequilibrium) studies are most successful when the disease is (mostly) caused by a single mutation

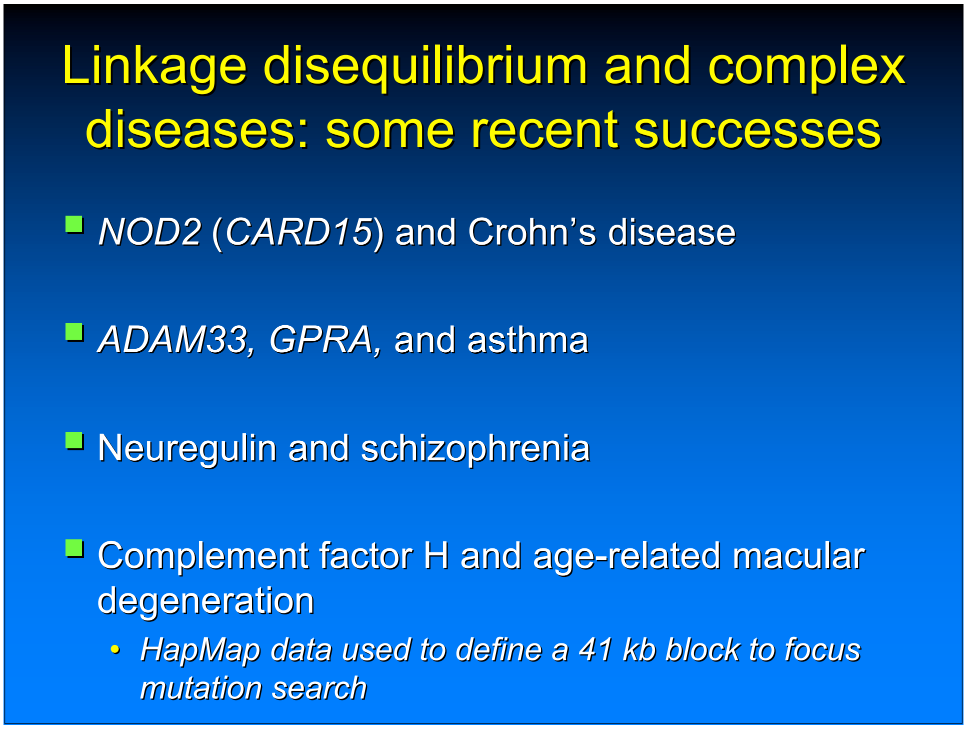

A b c D E f g H I J k l M N
a B C d e F G h i j K L m n
a b C D e F G h i J K l m N
A B c d E f g H I j k L M n
A b c D E f g H i j K L M n

Multiple disease-causing mutations can pose problems for association analysis


A b c D E f g H I J k l M N
a B C d e F G h i j K L m n
a b C D e F G h i J K l m N
A B c d E f g H I j k L M n
A b c D E f g H i j K L M n

How can we reduce heterogeneity?

- Define the trait consistently and accurately
- Identify subtypes
  - Early onset
  - Severe expression
  - Atypical expression
- Use strict, narrow population definitions



Linkage disequilibrium and complex diseases: some recent successes

- *NOD2* (*CARD15*) and Crohn’s disease
- *ADAM33, GPRA,* and asthma
- Neuregulin and schizophrenia
- Complement factor H and age-related macular degeneration
  - *HapMap data used to define a 41 kb block to focus mutation search*