Genetics 210: Personalized Medicine and Genomics

It's far more important to know what person the disease has than what disease the person has.

-Hippocrates

For: MDs, PhDs and curious students

Spring term. Tue 2:15 – 4:05

Thur. 2:15-4:05

LKSC 101

Genotyping : $25 copay

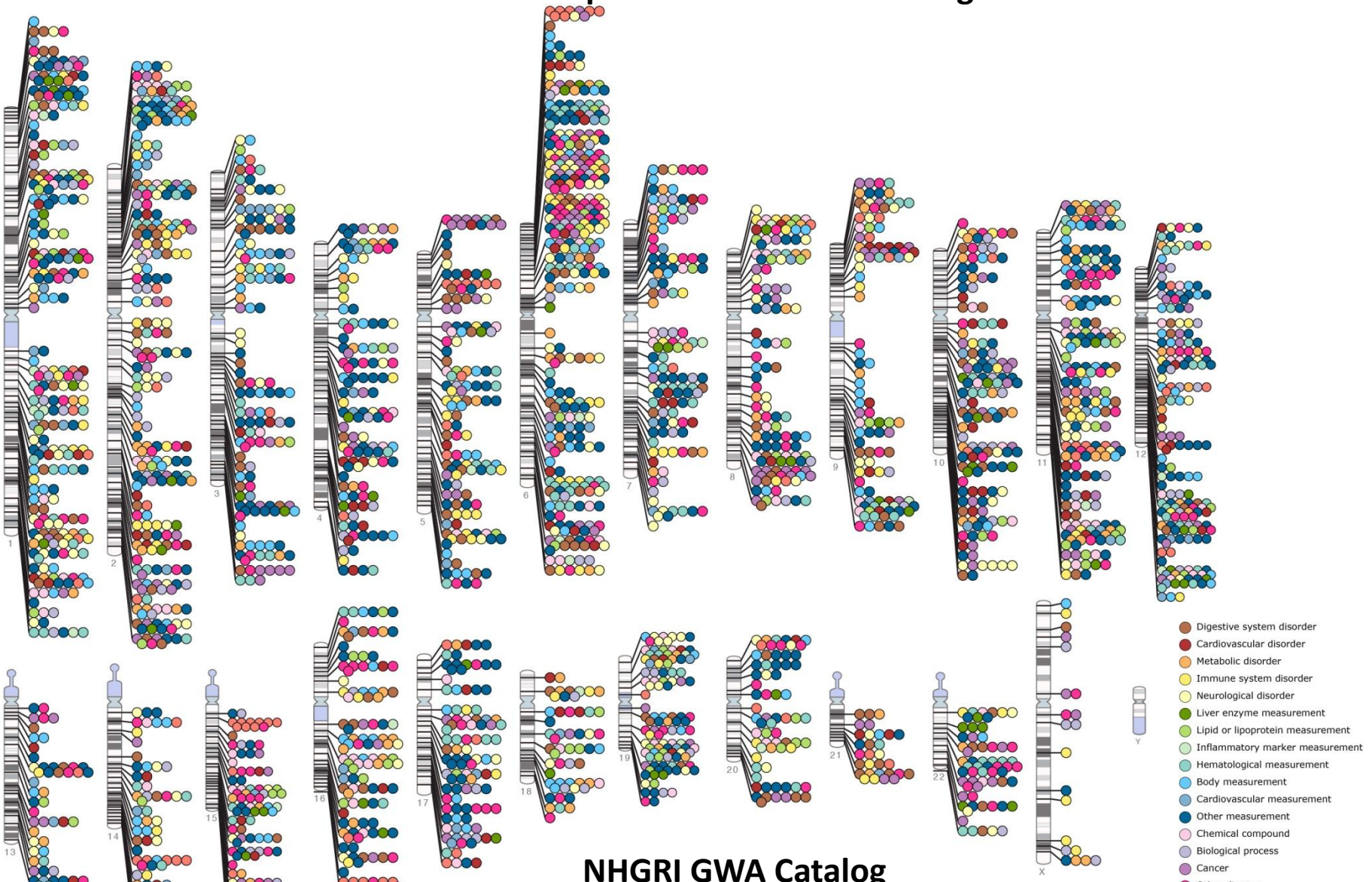
Gene210.stanford.edu: info and FAQs

Course Staff

- http://stanford.edu/class/gene210/web/html/contact.html
- Course Organizers:
  - Stuart Kim (Dev. Bio., Genetics)
  - Aaron Gitler (Genetics)
  - Rosalind Chuang (Neurology)
- TAs:
  - Roxana Daneshjou (Genetics)
  - Gokul Ramaswami (Genetics)
  - Greg Roe (Genetics)

Human Genetic Diversity

Published Genome-Wide Associations through 07/2012
Published GWA at $p \leq 5X10^{-8}$ for 18 trait categories

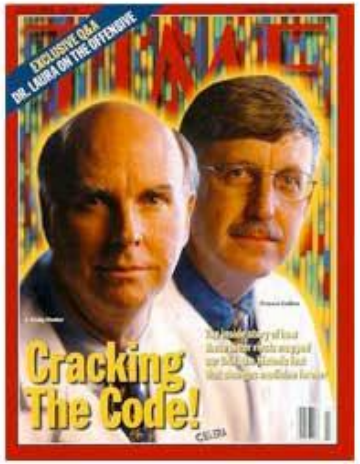


NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

National Human Genome Research Institute

EMBL-EBI

2000



0.1% x 3.3 billion
= 3,300,000 bp of differences

"I believe one of the great truths to emerge from this triumphant expedition inside the human genome is that in genetic terms, all human beings, regardless of race, are more than 99.9 percent the same."
President Bill Clinton, June 26, 2000, The White House East Room

History

Joint Genotyping Task Force

Charles Prober Dean
Russ Altman Genetics
Pat Brown Biochem.
Mike Grecius Neur.
Carlos Bustamente Gen.
Ralph Horwitz Psych
Anne James Legal Counsel
Stuart Kim Dev. Bio.
Phil Lavori HRP
Kelly Ormond Genetics
Mike Snyder Genetics
Keyan Salari Med. School

Hank Greely Law School
Clarence Braddock Med School
Gil Chu Biochem
Sean David Med. School
Harry Greenberg Dean
Louanne Hudgins Epidemiology
Jesse Karmazin Med. School
Mark Krasnow Biochem
David Magnus Cen. BME
Alan Schatzberg Psych.
Atul Butte BMI
Mildred Cho Pediatrics

Personal Genotyping

- Voluntary. You can use a public genome file instead of your own.
- Confidential – instructors will not know who opted to be genotyped.
- Private – Your own DNA information will not be revealed.
- Counseling - genetic counseling via 23andMe and medical/psychological counseling via Dr. Alan Schatzberg (Psychology, Stanford).

Course Schedule

- http://stanford.edu/class/gene210/web/html/schedule.html
- Activities
  - GWAS
  - Neandertal
  - Human positive selection
  - Who done it?
  - Ethics debate
- Presentations
  - Euan Ashley
  - Russ Altman
  - Steve Montgomery
  - Mike Snyder
- Spokespeople
  - Robin Starr
  - Kristen Powers
  - Katie Moser

Course Requirements

http://stanford.edu/class/gene210/web/html/course_requirements.html

- Problem Sets (20%)
  - Problem set 1. Out April 4. Due April 18.
  - Problem set 2. Out April 18. Due May 2.

Course Requirements

http://stanford.edu/class/gene210/web/html/course_requirements.html

- Projects (40%) Choose one of the following projects. Email **gene210.stanford@gmail.com** by May 2 with your choice.
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- 1. Write-up
  - a. One page write up of association of how a SNP is linked with a particular trait. The format is the same as used at SNPedia.com.
- 2. Special Project
  - In the past, some students have found a specific interest in some aspect of Personalized Medicine. This may come from your interest in some aspect of your own genetics, the ethics of genetic testing, or entrepreneurial possibilities in Personalized Medicine. You may come up with an individualized project for class credit by discussing your idea with one of the course directors.
-

Course Requirements

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- Final Exam (40% credit) take home.
  - Scenario is that you are an MD diagnosing a patient.
  - You will be given the genotypes of a hypothetical family. The final will have various scenarios.
  - Extra credit. (10%)
    - a. You will be given the genotypes of 7 people (SK, KK, RT, NT, NZ, MPS, GC).
    - b. You will be told ancestry and specific traits for these 7 people.
    - c. You need to match the genotype with the person.

Course Requirements

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- Super-projects
  - In the past, some students have taken this introductory class even though they are highly advanced in human genetics and bioinformatics. These students can do a more advanced project by consulting one of the course instructors. Students that undertake a super-project do not need to take the final exam. Possible super-projects topics include:
    - a. Annotate whole-genome sequence for Stuart Kim or Aaron Gitler (adopted).
    - b. Write a grant for Kaiser-Permanente GWAS (n=110,000 patients)
    - c. Analyze exome sequence data from ALS patients
    - d. Write an algorithm for choosing minimal n number of people to sequence to get all sequence data in a population

Volunteers?

The Stanford Daily

Alexis Garduno, agarduno@stanford.edu

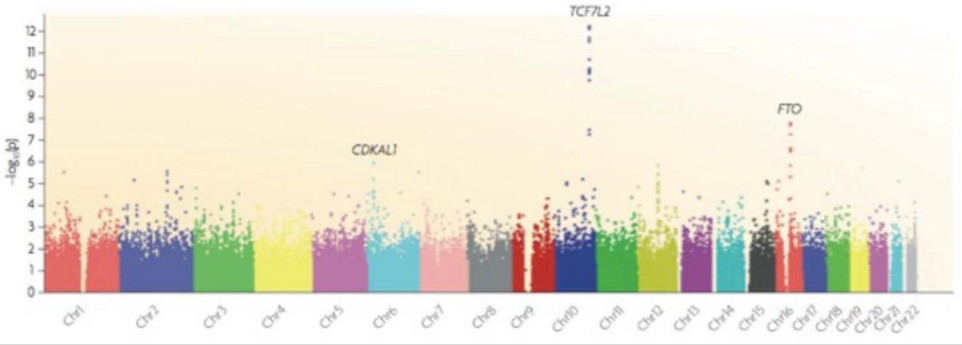
Chicago Medicine

Howard Wolinsky, howard.wolinsky@gmail.com

1. Natural variation in the human genome

2. Genetic Association & Linkage Disequilibrium

3. Genome-wide association studies



Steve Quake

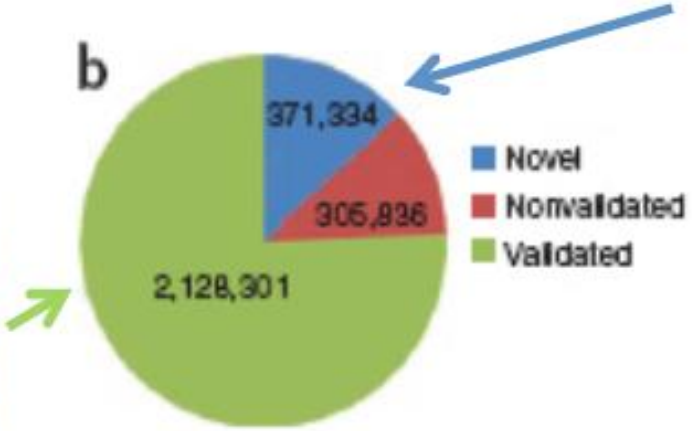
nature biotechnology

LETTERS

Single-molecule sequencing of an individual human genome

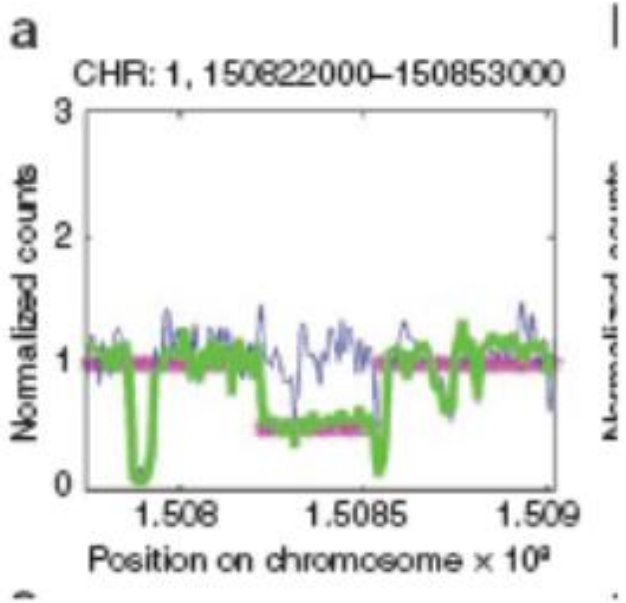
Dmitry Pushkarev[1,2], Norma F Neff[1,2] & Stephen R Quake[1]

Nature Biotech 27, 847, 2009



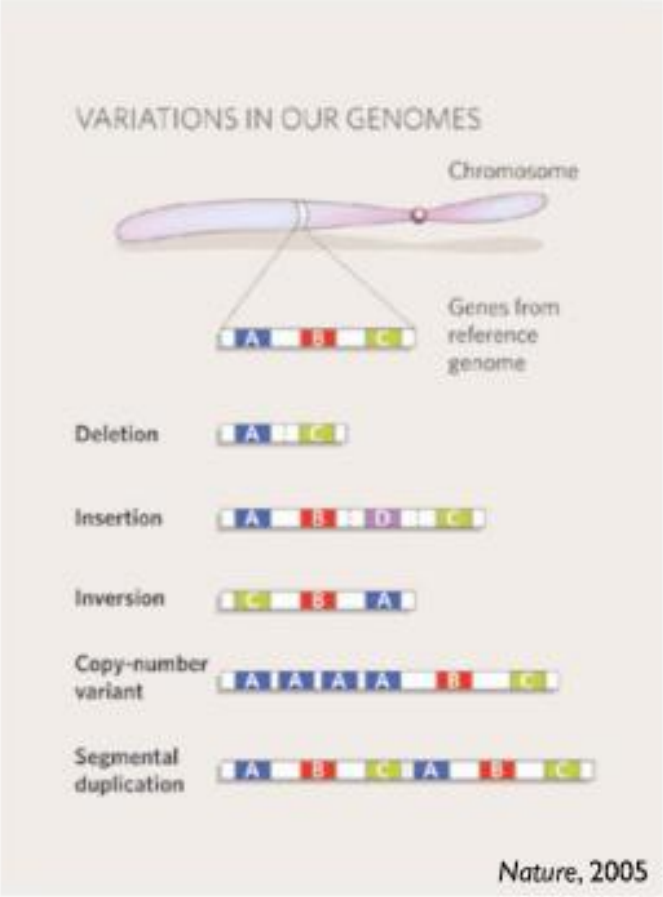
- 2.8 Million SNPs
  - 371 Thousand SNPs (13%) are novel

Copy number variation



- 752 copy number variations
- 16 Mb total

Human Genetic Variation



Nature, 2005

Structural variation

- 12% of our genome
- thousands of genes, disease loci, functional elements
- likely role in phenotypic variation and human disease

Redon *et al. Nature*, 2006

Genetic variation for a simple trait

Chr12: ALDH2 - SNP rs671

```
...GGGCTGCAGGCATACACTGAAGTGAAAACTGTGAGTGTG
...GGGCTGCAGGCATACACTGAAGTGAAAACTGTGAGTGTG
... G  L  Q  A  Y  T  E  V  K  T  V  S  V
```

Genotype: G/G

Protein: functional

Phenotype: none

Chr12: ALDH2 - SNP rs671

```
... GGGCTGCAGGCATACACTGAAGTGAAAACTGTGAGTGTG
... GGGCTGCAGGCATACACTAAAGTGAAAACTGTGAGTGTG
... G  L  Q  A  Y  T E/K V  K  T  V  S  V
```

Genotype: A/G

Protein: 1/2 functional

Phenotype: alcohol flush reaction

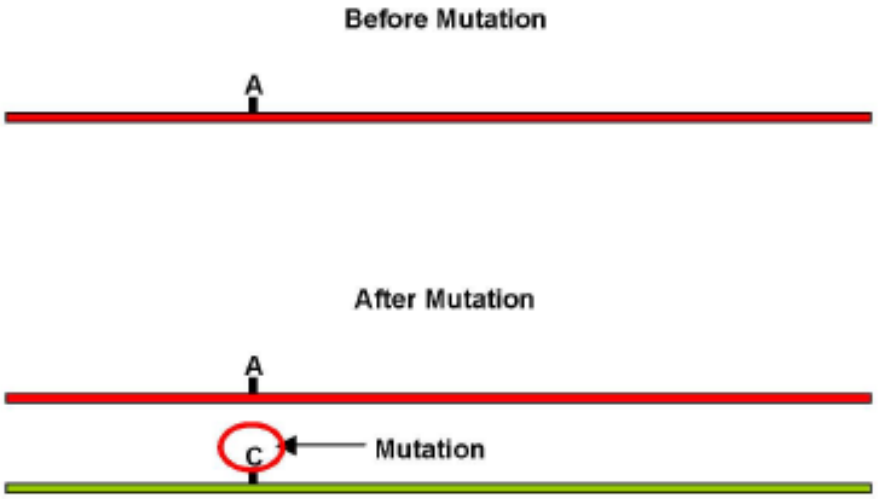
G allele functional
A allele missense (null)

CEU 100% G
YRI 100% G
CHB/JPT 76-84% G

Today ...

- We'll consider properties of pairs of alleles
- Haplotype frequencies
- Linkage equilibrium
- Linkage disequilibrium

Alleles that exist today arose through ancient mutation events…



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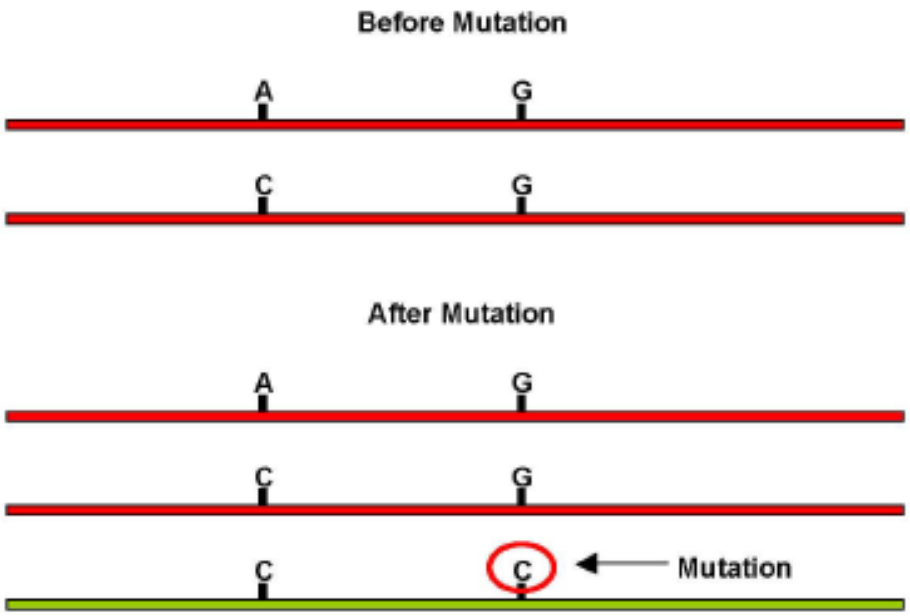
One allele arose first, and then the other...



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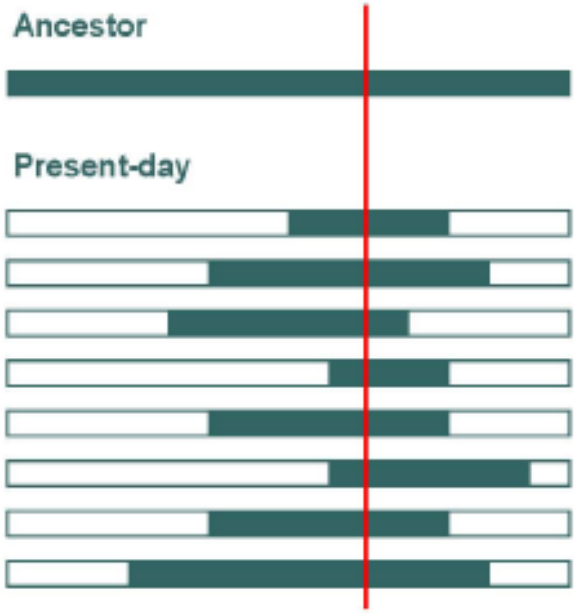
Recombination generates new arrangements for ancestral alleles

slide created by Goncarlo Abecasis

Linkage Disequilibrium

- Chromosomes are mosaics
- Extent and conservation of mosaic pieces depends on
  - Recombination rate
  - Mutation rate
  - Population size
  - Natural selection
- Combinations of alleles at very close markers reflect ancestral haplotypes



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Linkage

-Go to http://genotation.stanford.edu/

-Load your genome, race

-Under “presentations”, run “genetic linkage, part 1”

-Click “look up exercise”

-Click “submit my information”

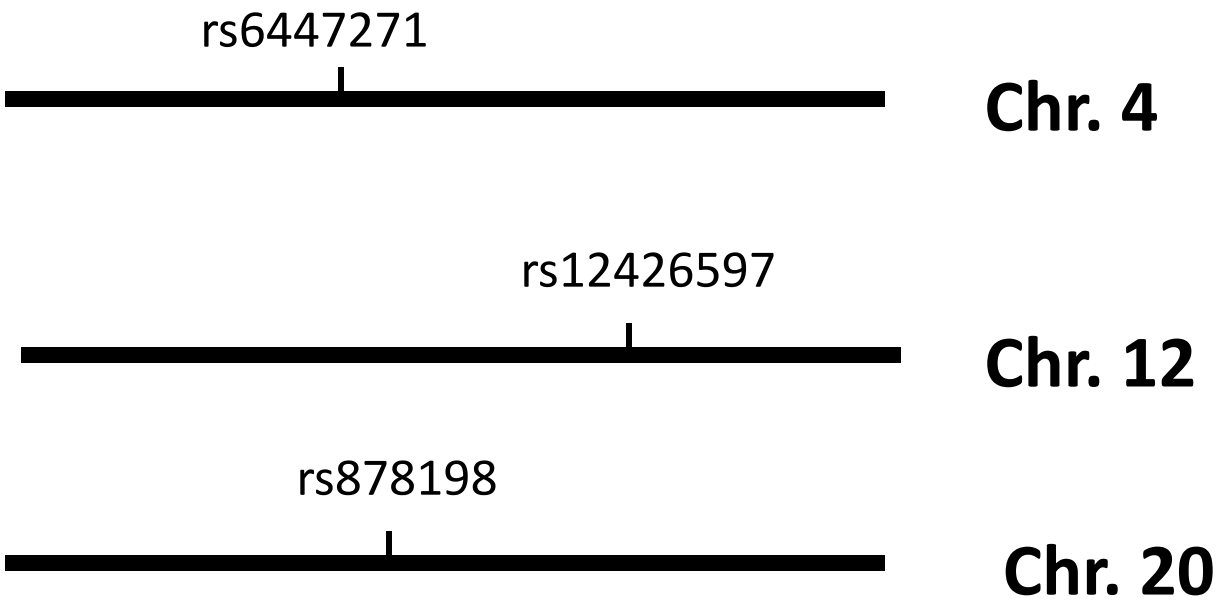
-Using the allele frequencies from class, calculate the chance of someone having your genotype.

-Compare the predicted genotype frequency to the observed genotype frequency in the class.

-Discuss.

-Repeat for parts 2 and 3. Discuss.

Genetic Linkage 1



Terminology

•**Genotype frequency**: If the SNPs segregate randomly, you can calculate this by multiplying each of the allele frequencies.

Linkage equilibrium: If the SNPs segregate randomly, they are said to be in equilibrium. If they do not segregate randomly, they are in linkage disequilibrium.

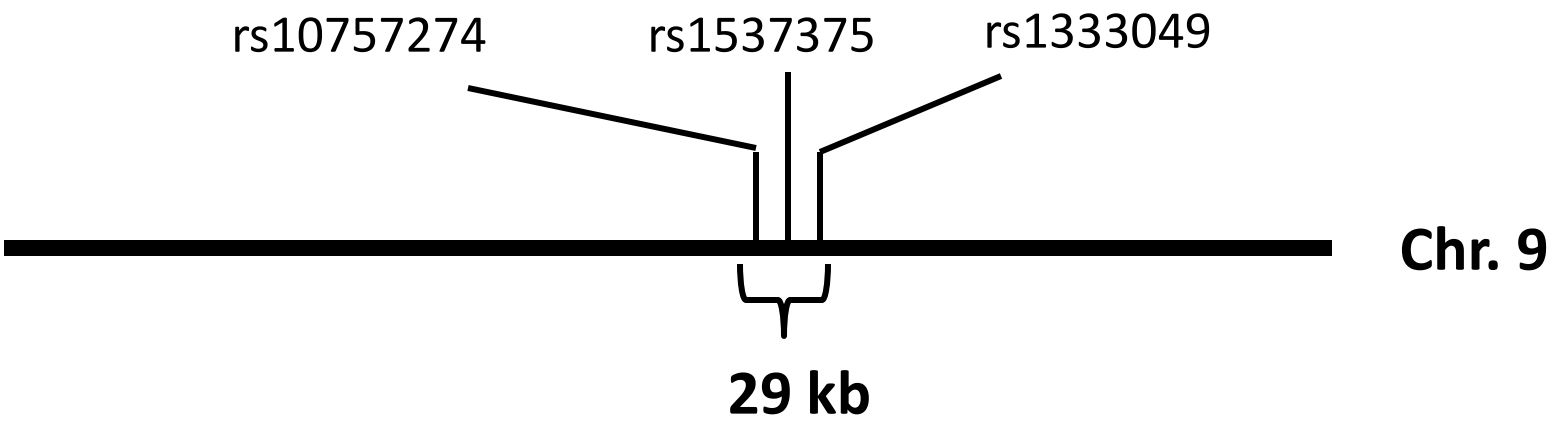
Haplotype: a set of markers that co-segregate with each other.

abc	or	abc	or	ABC
abc		ABC		ABC

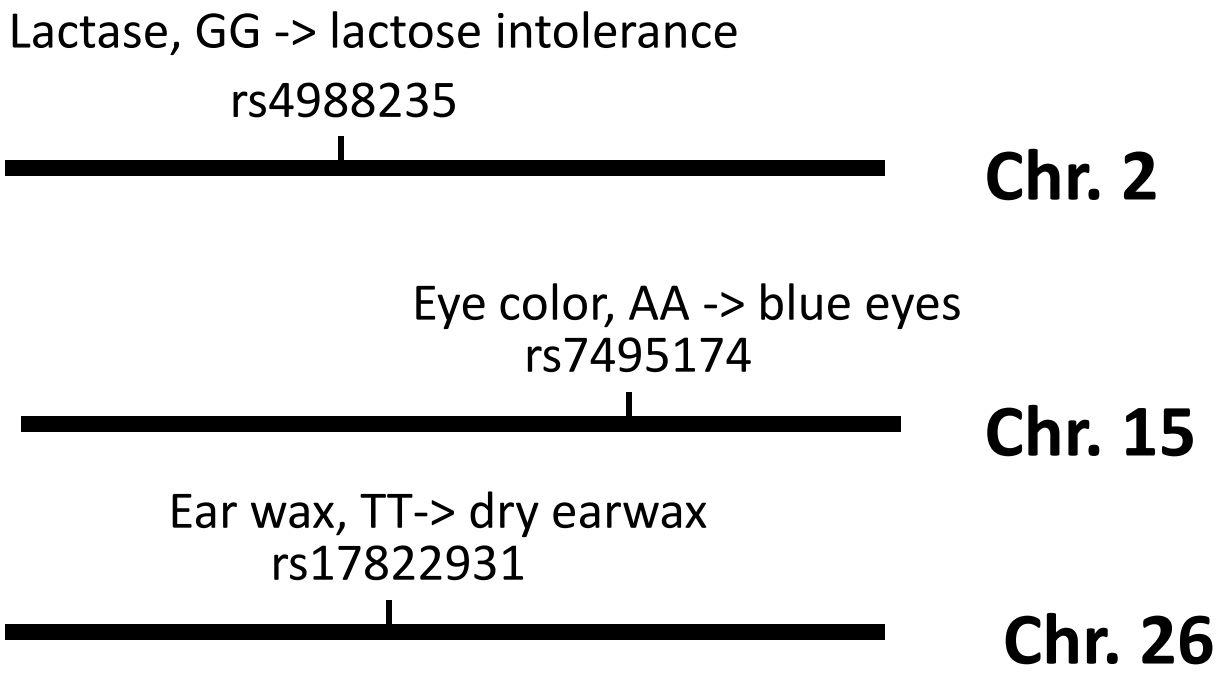
•**Phase**: refers to whether the alleles are in cis or in trans.

ab	or	aB
AB		Ab

Genetic Linkage 2



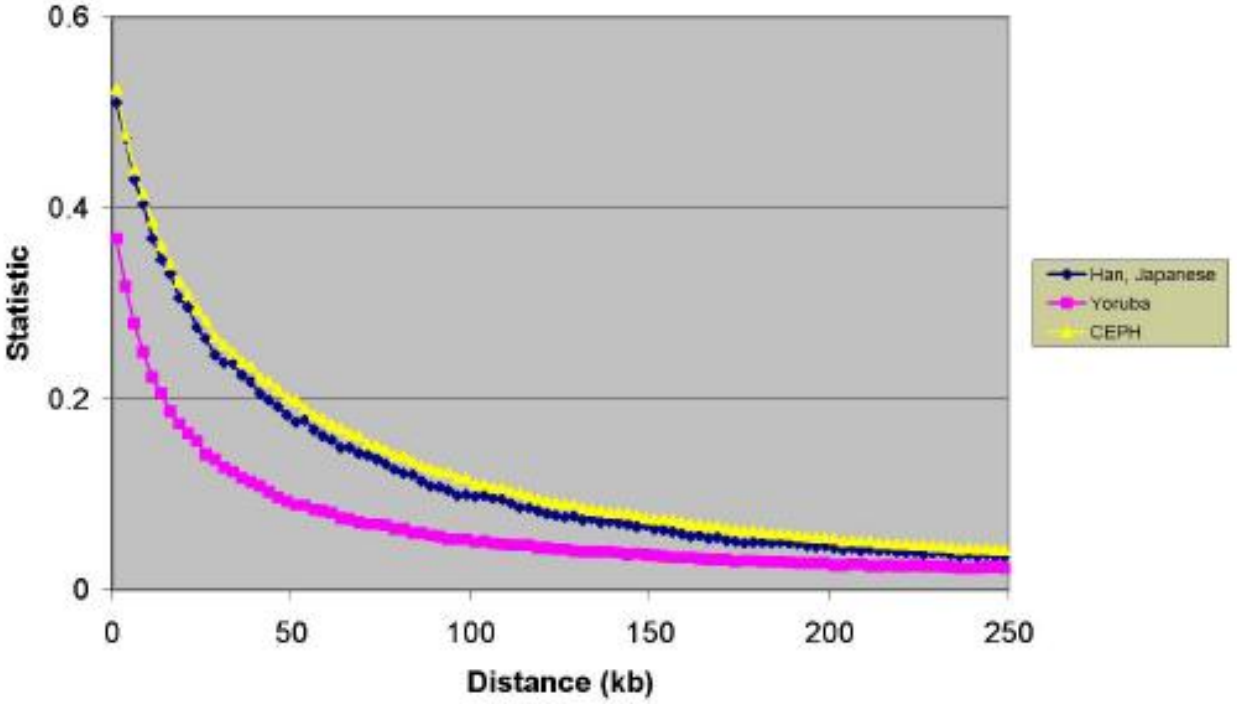
Genetic Linkage 3



Linkage

- The correlation between two markers (R) is a way to measure their linkage.
- R=1 indicates that the two markers are completely linked.
- R=0 indicates that the two markers segregate randomly.
- R^2 measures the loss of information when marker A is replaced by marker B.

Comparing Populations ...



LD extends further in CEPH and the Han/Japanese than in the Yoruba

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