CMSC423: Bioinformatic Algorithms, Databases and Tools
Lecture 16

Genetics

Reading assignment

- Chapter 13

Gene association studies

- Goal: identify genes/markers associated with disease
- Example: BRCA1 – associated with risk of breast cancer
- Lots of hype on the news recently: companies promise to "sequence" your genome and tell you:
  - likely ancestry
  - risk for disease
- Examples:
  - www.23andme.com
  - www.decodeme.com
  - and many others

First...definitions

- Genotype – genetic composition of our genome
- Phenotype – observable consequence of genotype – e.g. skin/hair color, IQ, disease state, etc.
- We have two copies of each chromosome (homologous chromosomes), each received from one of the parents
- Each gene can, thus, have two forms (alleles), e.g. A1/A2
- Each gene may be associated with a phenotype
- Dominant gene – phenotype of A1/A2 is the same as phenotype of A1/A1
- Recessive gene - otherwise

More definitions

- Genotype A/A is called homozygous (both chromosomes have the same allele)
- Genotype A/B is called heterozygous (mother and father's chromosomes disagree)
- Notes:
  - phenotypes not necessarily directly correlated with a single gene – polygenic traits
  - probability gene correlates with a phenotype – penetrance
  - link between genotype and phenotype can be qualitative (gene “form” matters) or quantitative (gene dosage matters)

Technology – what we measure?

- Definition of allele/genotype depends on what we can measure – constantly changing
- We are looking for things that differ within a population – polymorphic markers:
  - Restriction fragment length polymorphism (RFLP)– measures presence/absence of particular sites in the genome
  - Variable number tandem repeats (VNTR) – specific repeat elements that occur in different copy numbers
  - Single-nucleotide polymorphisms (SNPs) – single letter differences between chromosomes (>500,000 characterized)
  - Copy number variants (CNV) – genomic regions whose copy number differs between individuals

Allele frequencies

- Population genetics questions:
  - what alleles exist in a certain population?
  - what is the relative abundance of the alleles?
  - how “diverse” is a population?
- Given a locus (gene or genomic region), assume there are K possible alleles in a population and allele j occurs with frequency p_j
- How “uniform” is the locus in the population? Likelihood two random individuals have same allele

$$\text{homzygosity } F = \sum_{i=1}^{K} p_i^2$$

Allele frequencies...

- Usually we focus on the differences:

$$\text{heterzygosity } H = 1 - F = 1 - \sum_{i=1}^{K} p_i^2$$

- Interesting tidbit – most variation occurs within populations rather than between, e.g. two Africans are more different from each other than the average African is from the average Chinese (see book for details)
- However, allele frequencies can be used to infer population membership for an individual

Who am I?

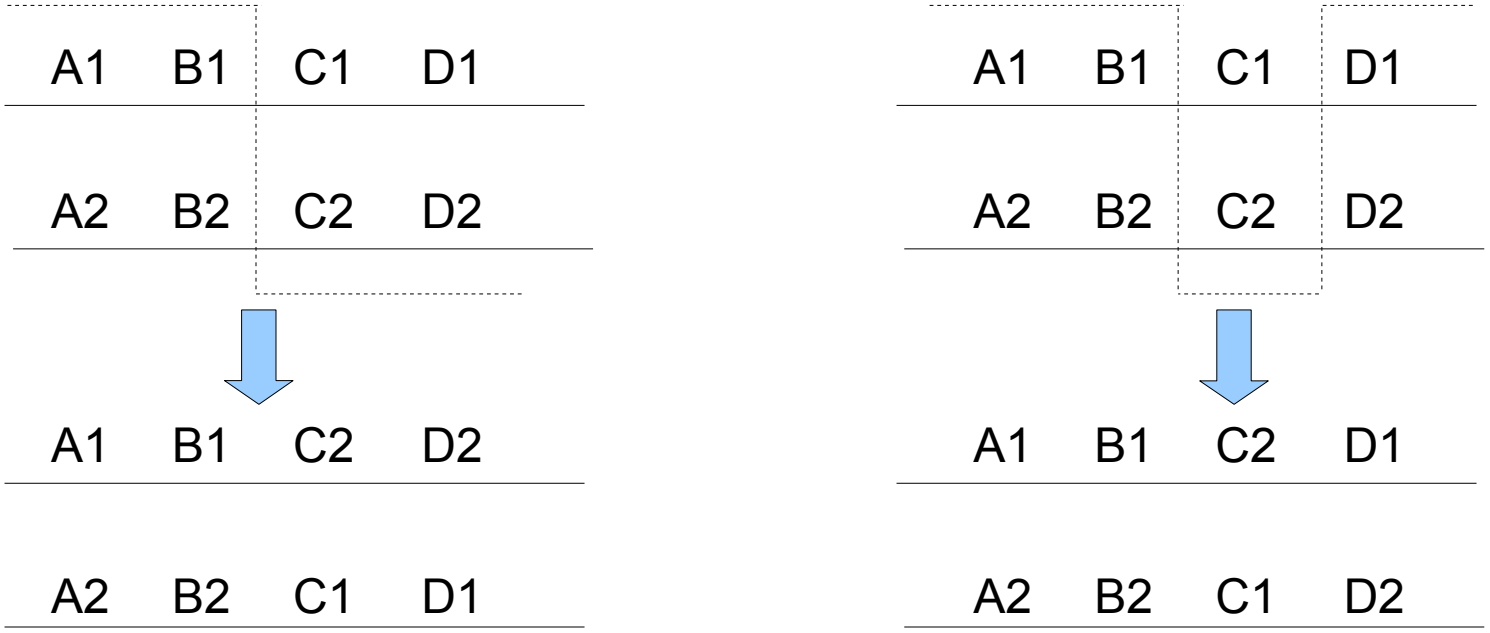
- My alleles are A_1, B_2, C_1, D_3 (assume homozygous for clarity)
- Am I European or Asian?
- Need to know:
  p_{A1}^{Europe}, p_{B2}^{Europe}, p_{C1}^{Europe}, p_{D3}^{Europe}
  p_{A1}^{Asia}, p_{B2}^{Asia}, p_{C1}^{Asia}, p_{D3}^{Asia}
- p(me, European) = $(p_{A1}^{Europe})^2 X (p_{B2}^{Europe})^2 X (p_{C1}^{Europe})^2 X (p_{D3}^{Europe})^2$
- similarly for p(me, Asian)
- if p(me, European) > p(me, Asian) I can infer that I have European ancestry

Who am I?

- Inferring ancestry as described is overly-simplistic
- Can do more fancy statistics
- However: any statistical approach is error prone – answer is associated with level of confidence, i.e. probability answer is wrong (remember P-values?)
- Beware of anyone who claims to infer your ancestry from genotype
- Beware of anyone who claims to infer disease susceptibility from genotype - need genetic/risk counselors not companies providing information for "entertainment purposes"

Recombination

- Genetic change not only caused by mutations
- Recombination – DNA “jumps” between homologous chromosomes due to cross-over events



Association studies

- The set of alleles on a same chromosome – haplotype
- If a particular allele of a gene is always associated with a phenotype (disease) – is this gene causing the disease?
- Most likely – gene is associated/nearby with the gene causing the disease (their alleles always appear on the same haplotype)
- Due to recombination a set of original haplotypes rapidly becomes broken apart
- How likely is it that two alleles remain on the same haplotype (are linked) during evolution?

Linkage analysis

- Preservation of linkage depends on distance between the genes and rate of recombination
- Given two genes (A, B) – how can we estimate whether recombination occurred between them?
- How likely is it that A_1 and B_1 are both on the same haplotype by chance?

  $p(A_1)p(B_1)$

- How different is this from the observed ratios? - Linkage Desequilibrium

  $D = p(A_1B_1) – p(A_1)p(B_1)$
  $D = p(A_2B_2) – p(A_2)p(B_2)$
  $D = p(A_1B_1)p(A_2B_2) - p(A_1B_2)p(A_2B_1)$

Linkage analysis

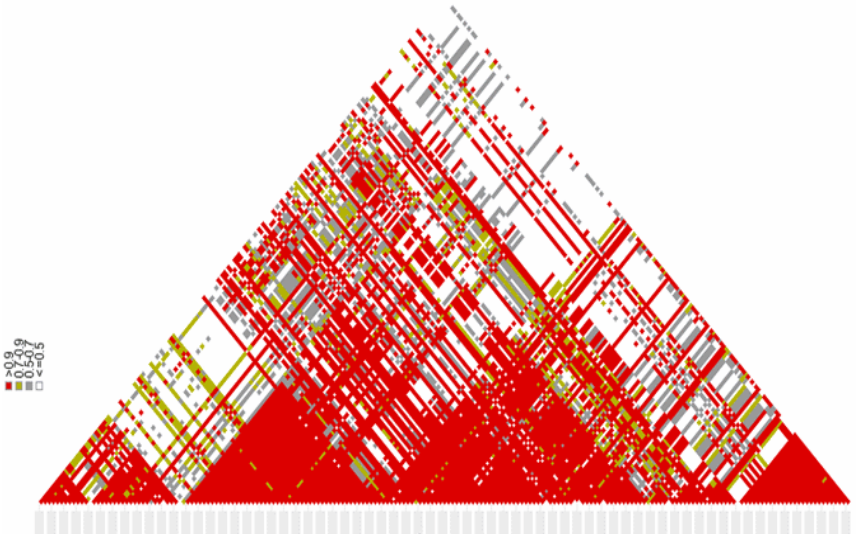
- Linkage desequilibrium usually measured as ratio to maximum possible desequilibrium - D/Dmax

  $Dmax = \min(p(A_2)p(B_1), p(A_1)p(B_2))$ if $D > 0$

  $Dmax = \min(p(A_1)p(B_1), p(A_2)p(B_2))$ if $D < 0$

- Another measure – Pearson's correlation coefficient

  $r^2 = D^2/(p(A_1)p(A_2)p(B_1)p(B_2)$



Additional resources

- www.hapmap.org
- www.1000genomes.org
- www.personalgenomes.org
- http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim

Homework

- Prove the equalities on slide 13 (D = ...)
- Derive the formula for Dmax on slide 14 (problem 3.5 in book)

- Due Tuesday Nov 4 – submit by E-mail to me and Mohammad