Genetics or Genomics?

- genetics: study single genes or a few genes
  - first identify mutant organism with change of interest
  - characterize effects of mutation
  - but only a fraction of 30k human genes directly studied!
- genomics: genes as dynamics system
  - over space (chromosomes) & time (evolution)
  - gene interactions, biological networks
- gene ontology (www.geneontology.org)
  - molecular function: what gene does
  - biological process: objective via assemblies of molecular functions
  - cellular component: of anatomical structure or gene product group
- (www.genomicglossaries.com)

1 General Biology Relevant to QTL

why do QTL mapping?

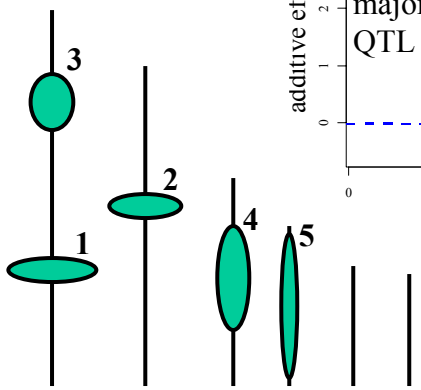
- **agriculture:**
  - crop/breed improvement
  - pest/pathogen resistance
  - marker assisted selection/introgression
  - bypass transgenics/GMOs?
- **biomedicine:**
  - unravel complex diseases
  - function of biochemical networks
  - genotype-specific therapy
- **evolution:**
  - basic biological science
  - model systems & comparative genomics
  - interplay of genetics & ecology

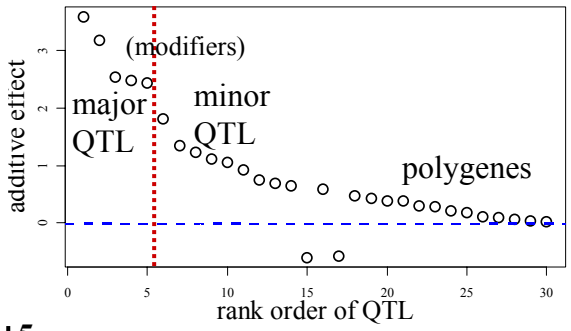
What is a QTL?

- QTL = quantitative trait locus (or loci)
  - trait = phenotype = characteristic of interest
  - quantitative = measured somehow
    - qualitative traits can often be directly mapped
    - quantitative traits not readily mapped
  - locus = location in genome affecting trait
    - gene or collection of tightly linked genes
    - some physical feature of genome

Pareto diagram of QTL effects

major QTL on linkage map





Components of QTL

- What is a phenotype?
- Meiosis and recombination
  - common experimental crosses: BC and F2
- What is a QTL?
  - central dogma of biology
  - relating phenotype to genotype
- QTL success stories?

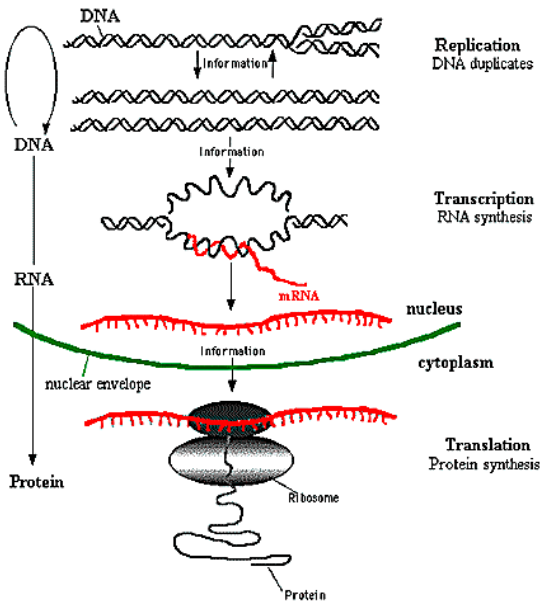
What is a phenotype or trait?

- phenotype = measured characteristic
- phenotype examples
  - size, color, disease resistance score
  - developmental times (flowering, disease onset)
  - number of offspring, number of tumors
  - response to stimuli (shock, loud sound)
  - changes in internal biochemistry
- simple vs. complex phenotypes
  - simple: one gene, highly heritable
  - complex: multiple genes, environment important

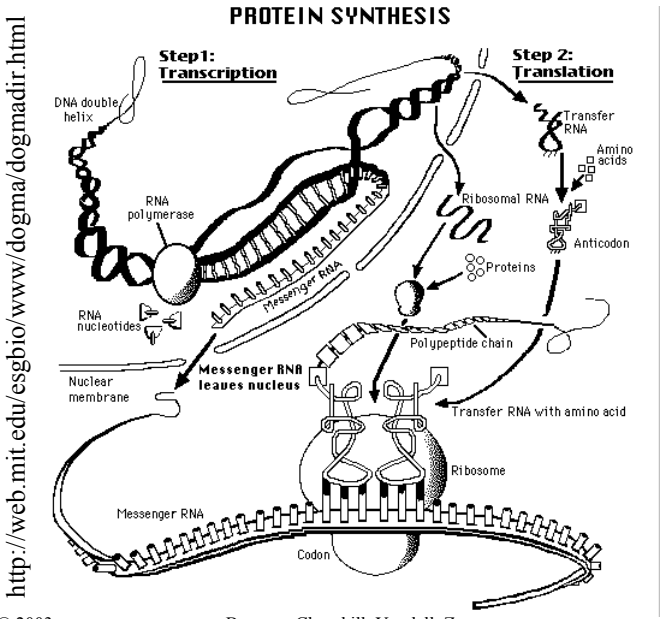
Dogma of DNA

- DNA → mRNA → protein
  - (www.accessexcellence.org/AB/GG/central.html)
- protein → metabolites → network cascade
  → "latent" phenotype → measured phenotype
  (www.jic.bbsrc.ac.uk/corporate/Facilities/metabolomics.html)
- How to relate changes in DNA to changes in measured phenotype?
- MIT Dogma Show
  - (web.mit.edu/esgbio/www/dogma/dogmadir.html)

http://www.accessexcellence.org/AB/GG/central.html



The Central Dogma of Molecular Biology

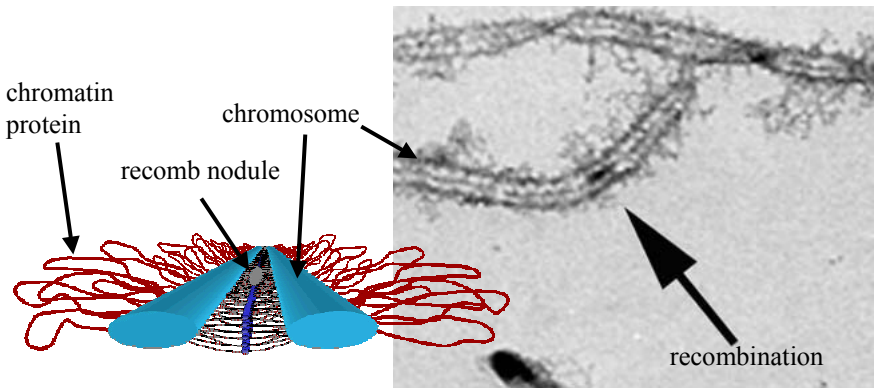


http://web.mit.edu/esgbio/www/dogma/dogmadir.html

What is Meiosis?

- meiosis = two consecutive cell divisions
  - (diploid) chromosomes resegregate
  - 2 chromatids each for 2 chromosomes
- Meiosis 1
  - prophase I
    - homologous chromosomes pair (bivalent) and align
    - form synaptonemal complex
    - crossing over can occur at recombination nodules
    - chiasmata result from crossover event
  - prometaphase 1, metaphase 1, anaphase 1, telophase 1
    - Chromosomes separate into 2 daugher cells
- Meiosis 2
  - chromatids separate into 4 daughter cells
- Quicktime cartoon of meiosis:
  www.biology.arizona.edu/cell_bio/tutorials/meiosis/page3.html

Prophase 1 Synaptonemal Complex



DG Peterson http://www.msstate.edu/research/mgel/meiosis.htm

recombination & crossovers

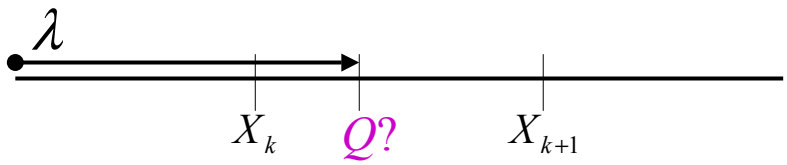
- crossovers occur in synaptonemal complex
  - physical process during meiosis
  - cannot observe except using cytology
- recombination is between genetic markers
  - observe change in phase at genetic markers
  - infer odd number of crossover events between
- McPeek presentation

  stat-www.berkeley.edu/users/sandrine/ PH296.F02/Disc/linkage.pdf

recombination model $\text{pr}(Q|X,\lambda)$

- locus λ is distance along linkage map
  - identifies flanking marker region
- flanking markers provide good approximation
  - map assumed known from earlier study
  - inaccuracy slight using only flanking markers
    - extend to next flanking markers if missing data
  - could consider more complicated relationship
    - but little change in results

$$\text{pr}(Q|X,\lambda) = \text{pr}(\text{geno} \mid \text{map, locus}) \approx \text{pr}(\text{geno} \mid \text{flanking markers, locus})$$

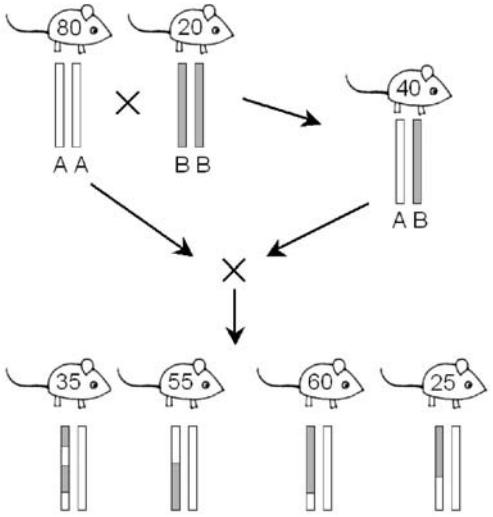


common experimental designs

- inbred parent lines P1, P2 (homozygous)
- F1 = P1 x P2 (completely heterozygous)
- backcross
  - B1 = P1 x F1 or B2 = P2 x F1
    - 1:1 expected ratio of homozygous to heterozygous loci
  - observe recombinations in F1 gametes
    - linkage leads to local patterns of homo- & hetero-zygous
  - parental background can affect phenotype
- F2 intercross
  - F1 selfing (plants) or brother-sister mating
  - recombinations possible for both gametes

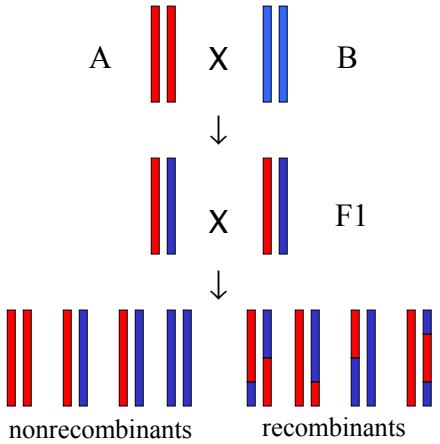
backcross experiment

- 2 inbred strains A, B
  - genotypes AA and BB
  - differ in trait
- cross to for F1
  - genotype AB
- backcross to A
  - genetic variation
    - AA : AB
  - recombination in F1
    - examine loci pairs
    - rare double recomb
- Goal: predict phenotype
  - find genomic regions
- from Broman (2000)



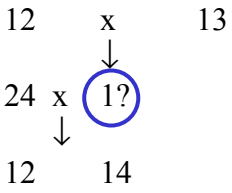
F2 intercross experiment

- cross A and B
- F1 offspring
  - All genotype AB
  - 2 meioses in F1
- F2 intercross
  - recombinants from both parents
  - 1:2:1 ratio
    - AA : 2 AB : BB
  - additive/dominance
- same basic goal
  - map genome regions
  - influencing phenotype



why restrict to inbred lines?

- simplified genetics
- common design
  - easy to conduct
- good power
  - for "coarse" map
  - but not fine map



what is missing genotype?