Quantitative Genomics and Genetics

BTRY 4830/6830; PBSB.5201.03

Lecture 15: Introduction to Quantitative Genetic Inference

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March 16, 2023 (Th) 8:05-9:20

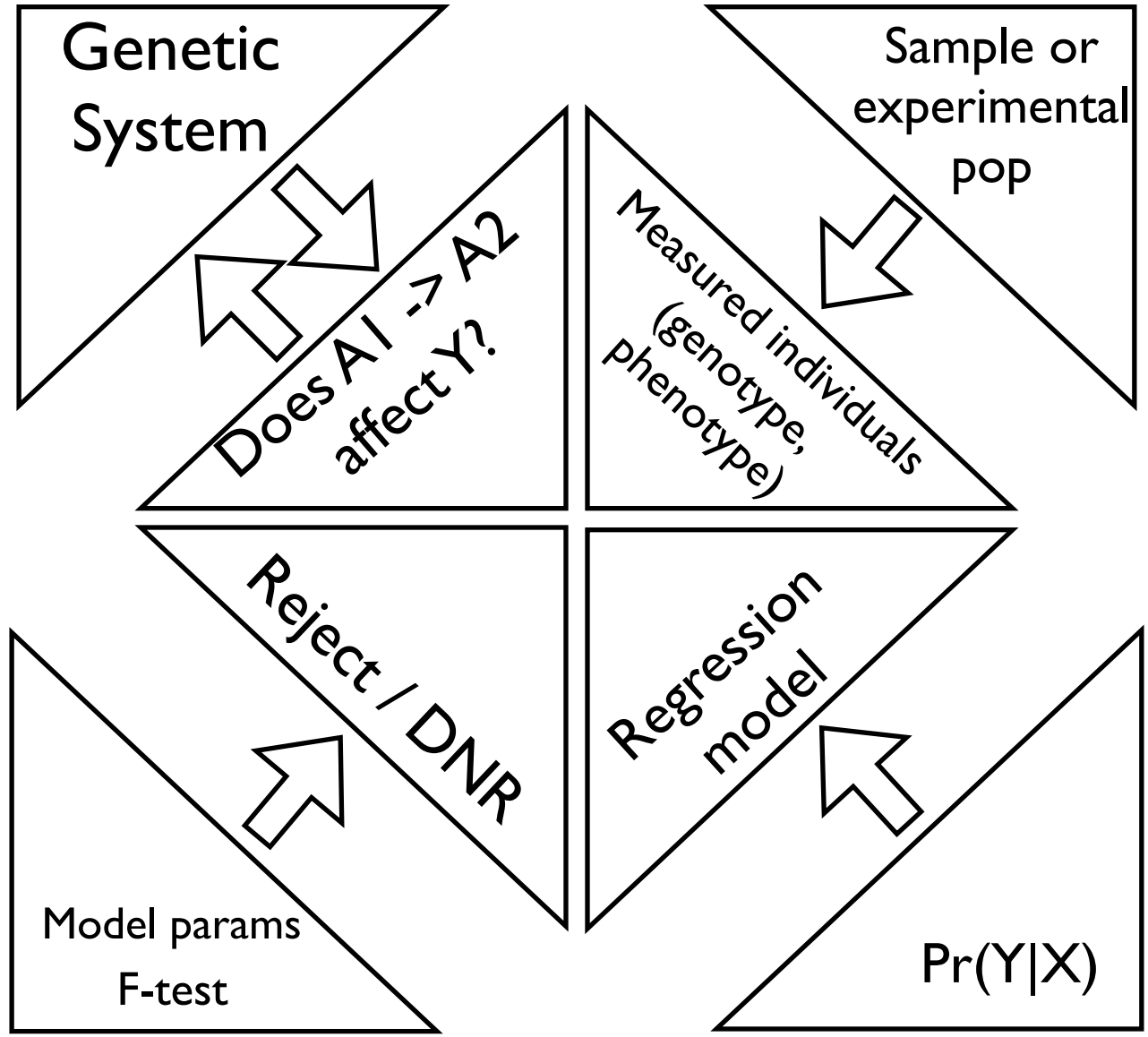
Announcements

- For those in NYC taking computer lab Thurs (TODAY!)
  - Changed to 5:30-6:30pm every Thurs
  - We WILL offer a zoom option
  - TODAY (!!) we may only have a zoom option (stay tuned…)
- We will have office hours
  - Tomorrow (March 17) 12-2pm
  - Mon, March 27 (TBA)
- Homework #4
  - Due 11:59pm March 27
  - WE WILL COVER THE MATERIAL FOR QUESTION #2 during the next three lectures, two computer labs, and two office hours
- Lectures next week (March 21 and March 23) will be by zoom (!!)

Summary of lecture 15: Introduction to Genetic Inference

- Last lecture, we completed our general discussion of genetic modeling and began discussing genetic inference
- Today, we will complete our initial discussion of genetic inference!

Conceptual Overview



Review: Genetic system

- **causal mutation** - a position in the genome where an experimental manipulation of the DNA would produce an effect on the phenotype under specifiable conditions
- Formally, we may represent this as follows:

$$A_1 \rightarrow A_2 \Rightarrow \Delta Y | Z$$

- Note: that this definition considers "under specifiable" conditions" so the change in genome need not cause a difference under every manipulation (just under broadly specifiable conditions)
- Also note the symmetry of the relationship
- Identifying these is the core of quantitative genetics/genomics (why do we want to do this!?)
- What is the perfect experiment?
- Our experiment will be a statistical experiment (sample and inference!)

Review: Genetic inference I

- For our model focusing on one locus:

$$Y = \beta_\mu + X_a\beta_a + X_d\beta_d + \epsilon$$

$$\epsilon \sim N(0, \sigma^2_\epsilon)$$

- We have four possible parameters we could estimate:

$$\theta = \left[\beta_\mu, \beta_a, \beta_d, \sigma^2_\epsilon\right]$$

- However, for our purposes, we are only interested in the genetic parameters and testing the following null hypothesis:

$$H_0 : Cov(X_a, Y) = 0 \cap Cov(X_d, Y) = 0$$
$$H_A : Cov(X_a, Y) \neq 0 \cup Cov(X_d, Y) \neq 0$$

OR

$$H_0 : \beta_a = 0 \cap \beta_d = 0$$
$$H_A : \beta_a \neq 0 \cup \beta_d \neq 0$$

Review: Genetic inference II

- For notation convenience, we are going to use vector / matrix notation to represent a sample:

$$y_i = \beta_\mu + x_{i,a}\beta_a + x_{i,d}\beta_d + \epsilon_i$$

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} \beta_\mu + x_{1,a}\beta_a + x_{1,d}\beta_d + \epsilon_1 \\ \beta_\mu + x_{2,a}\beta_a + x_{2,d}\beta_d + \epsilon_2 \\ \vdots \\ \beta_\mu + x_{n,a}\beta_a + x_{n,d}\beta_d + \epsilon_n \end{bmatrix}$$

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} 1 & x_{1,a} & x_{1,d} \\ 1 & x_{2,a} & x_{2,d} \\ \vdots & \vdots & \ddots \\ 1 & x_{n,a} & x_{n,d} \end{bmatrix} \begin{bmatrix} \beta_\mu \\ \beta_a \\ \beta_d \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ \vdots \\ \epsilon_n \end{bmatrix}$$

$$\mathbf{y} = \mathbf{x}\beta + \epsilon$$

Review: Genetic estimation

- Let's look at the structure of this estimator:

$$\mathbf{y} = \mathbf{x}\beta + \epsilon$$

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} 1 & x_{1,a} & x_{1,d} \\ 1 & x_{2,a} & x_{2,d} \\ \vdots & \vdots & \ddots \\ 1 & x_{n,a} & x_{n,d} \end{bmatrix} \begin{bmatrix} \beta_\mu \\ \beta_a \\ \beta_d \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ \vdots \\ \epsilon_n \end{bmatrix}$$

$$MLE(\hat{\beta}) = (\mathbf{x}^{\mathrm{T}}\mathbf{x})^{-1}\mathbf{x}^{\mathrm{T}}\mathbf{y}$$

$$MLE(\hat{\beta}) = \begin{bmatrix} \hat{\beta}_\mu \\ \hat{\beta}_a \\ \hat{\beta}_d \end{bmatrix}$$

Genetic hypothesis testing I

- We are going to test the following hypothesis:

$$H_0 : \beta_a = 0 \cap \beta_d = 0$$

$$H_A : \beta_a \neq 0 \cup \beta_d \neq 0$$

- To do this, we need to construct the following test statistic (for which we know the distribution!):

$$T(\mathbf{y}, \mathbf{x}_a, \mathbf{x}_d | H_0 : \beta_a = 0 \cap \beta_d = 0)$$

- Specifically, we are going to construct a likelihood ratio test (LRT)
- This is calculated using the same structure that we have discussed (i.e. ratio of likelihoods that take values of parameters maximized under the null and alternative hypothesis)
- In the case of a regression (not all cases!) we can write the form of the LRT for our null in an alternative (but equivalent!) form
- In addition, our LRT has an exact distribution for all sample sizes *n* (!!)

Genetic hypothesis testing II

- We now have everything we need to construct a hypothesis test for:

$$H_0 : \beta_a = 0 \cap \beta_d = 0$$

$$H_A : \beta_a \neq 0 \cup \beta_d \neq 0$$

- This is equivalent to testing the following:

$$H_0 : Cov(X, Y) = 0$$

- For a linear regression, we use the F-statistic for our sample:

$$F_{[2,n-3]}(\mathbf{y}, \mathbf{x_a}, \mathbf{x_d}) = \frac{MSM}{MSE}$$

- We then determine a p-value using the distribution of the F-statistic under the null:

$$pval(F_{[2,n-3]}(\mathbf{y}, \mathbf{x_a}, \mathbf{x_d}))$$

Genetic hypothesis testing III

- To construct our LRT for our null, we will need several components, first the predicted value of the phenotype for each individual:

$$\hat{y}_i = \hat{\beta}_\mu + x_{i,a}\hat{\beta}_a + x_{i,d}\hat{\beta}_d$$

- Second, we need the "Sum of Squares of the Model" (SSM) and the "Sum of Squares of the Error" (SSE):

$$SSM = \sum_{i=1}^{n}(\hat{y}_i - \overline{y})^2 \qquad SSE = \sum_{n=1}^{n}(y_i - \hat{y}_i)^2$$

- Third, we need the "Mean Squared Model" (MSM) and the "Mean Square Error" (MSE) with degrees of freedom (df) $df(M) = 3 - 1 = 2$ and : $df(E) = n - 3$

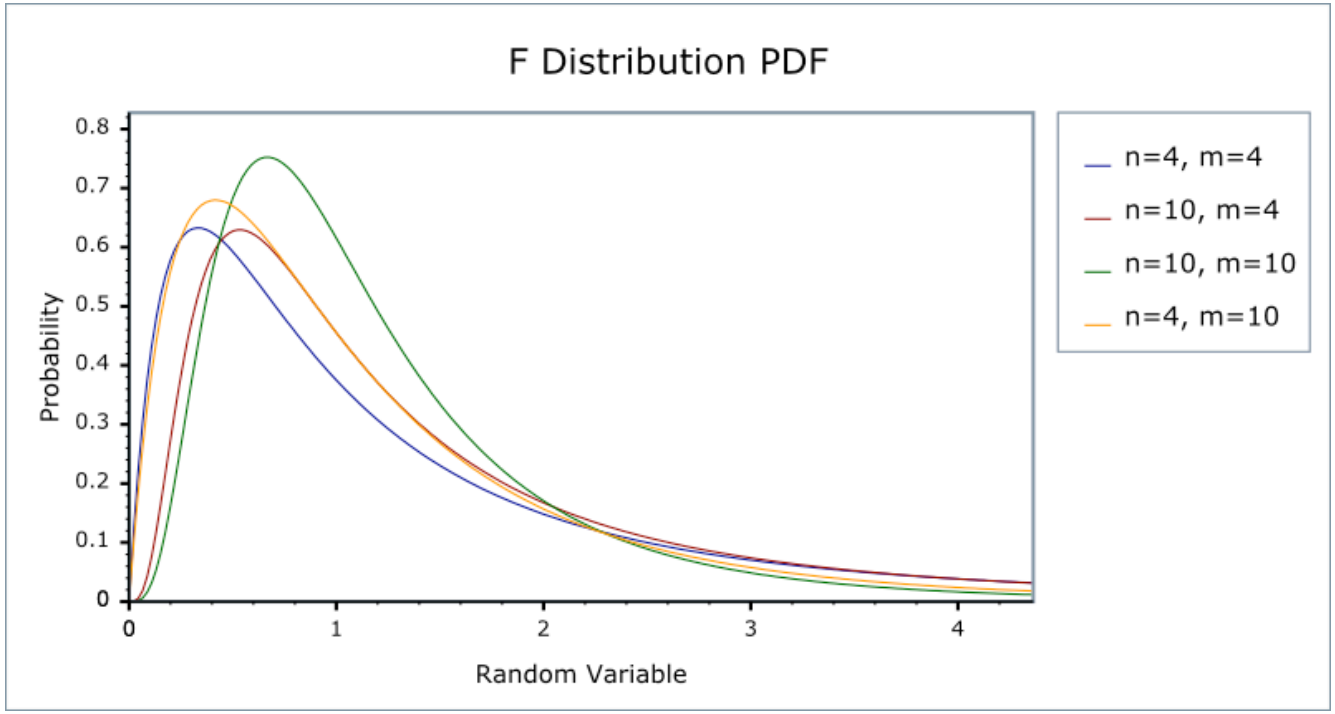
$$MSM = \frac{SSM}{df(M)} = \frac{SSM}{2} \qquad MSE = \frac{SSE}{df(E)} = \frac{SSE}{n-3}$$

- Finally, we calculate our (LRT!) statistic, the F-statistic with degrees of freedom [2, n-3]:

$$F_{[2,n-3]} = \frac{MSM}{MSE}$$

Genetic hypothesis testing IV

- In general, the F-distribution (continuous random variable!) under the H0 has variable forms that depend on d.f.:



- Note when calculating a p-value for the genetic model, we consider the value of the F-statistic we observe or more extreme towards positive infinite (!!) using the F-distribution with [2,n=3] d.f.

- However, also this is actually a two-tailed test (what is going on here (!?)

Genetic hypothesis testing V

- An F-statistic is a Likelihood Ratio Test (LRT) statistic after a simple (monotonic) transformation

$$F\text{−statistic} = f(\Lambda)$$

- Note that an F-statistic has an exact pdf under many conditions (note that we do not always produce a LRT that has an exact pdf that we can state easily)
- Also note that a t-test is actually an F-statistic (and therefore a transformed LRT) for a case where we are comparing the means of just two groups (when might this apply in genetic testing!?), similarly for a t-test of the slope of a regression)

Side-topic: Alternative (ANOVA) formulation I

- Note that we can construct an equivalent formulation to our *linear regression* using an *ANOVA* coding
- ANOVA stands for *ANalysis Of VAriance* and, despite the name, it is really a test of whether "means" of groups are different
- A genetic ANOVA model is the same as our linear regression, except the "dummy" variables are coded differently (everything else is the same!)

Side-topic: Alternative (ANOVA) formulation II

- Remember the independent (dummy) variable coding for a regression is:

$$X_\mu(A_1A_1) = 1, X_\mu(A_1A_2) = 1, X_\mu(A_2A_2) = 1$$

$$X_a(A_1A_1) = -1, X_a(A_1A_2) = 0, X_a(A_2A_2) = 1$$

$$X_d(A_1A_1) = -1, X_d(A_1A_2) = 1, X_d(A_2A_2) = -1$$

- The ANOVA coding is the following:

$$X_{A_1A_1}(A_1A_1) = 1, X_{A_1A_1}(A_1A_2) = 0, X_{A_1A_1}(A_2A_2) = 0$$

$$X_{A_1A_2}(A_1A_1) = 0, X_{A_1A_2}(A_1A_2) = 1, X_{A_1A_2}(A_2A_2) = 0$$

$$X_{A_2A_2}(A_1A_1) = 0, X_{A_2A_2}(A_1A_2) = 0, X_{A_2A_2}(A_2A_2) = 1$$

- The models corresponding to a linear regression and ANOVA are:

$$Y = X_\mu\beta_\mu + X_a\beta_a + X_d\beta_d + \epsilon$$

$$Y = X_{A_1A_1}\beta_{A_1A_1} + X_{A_1A_2}\beta_{A_1A_2} + X_{A_2A_2}\beta_{A_2A_2} + \epsilon$$

Side-topic: Alternative (ANOVA) formulation III

- For the ANOVA formulation, the parameters are:

$$\theta = [\beta_{A_1A_1}, \beta_{A_1A_2}, \beta_{A_2A_2}]$$

- And we test the null hypothesis:

$$H_0 : \beta_{A_1A_1} = \beta_{A_1A_2} = \beta_{A_2A_2}$$

$$H_A : \beta_{A_jA_k} \neq \beta_{A_lA_m} \qquad jk \neq lm$$

- Note that estimation (MLE) and the hypothesis test (F-test) construction are the same (=same equations)!!
- Why would we use an ANOVA formulation (what is the difference)?

Quantitative genomic analysis I

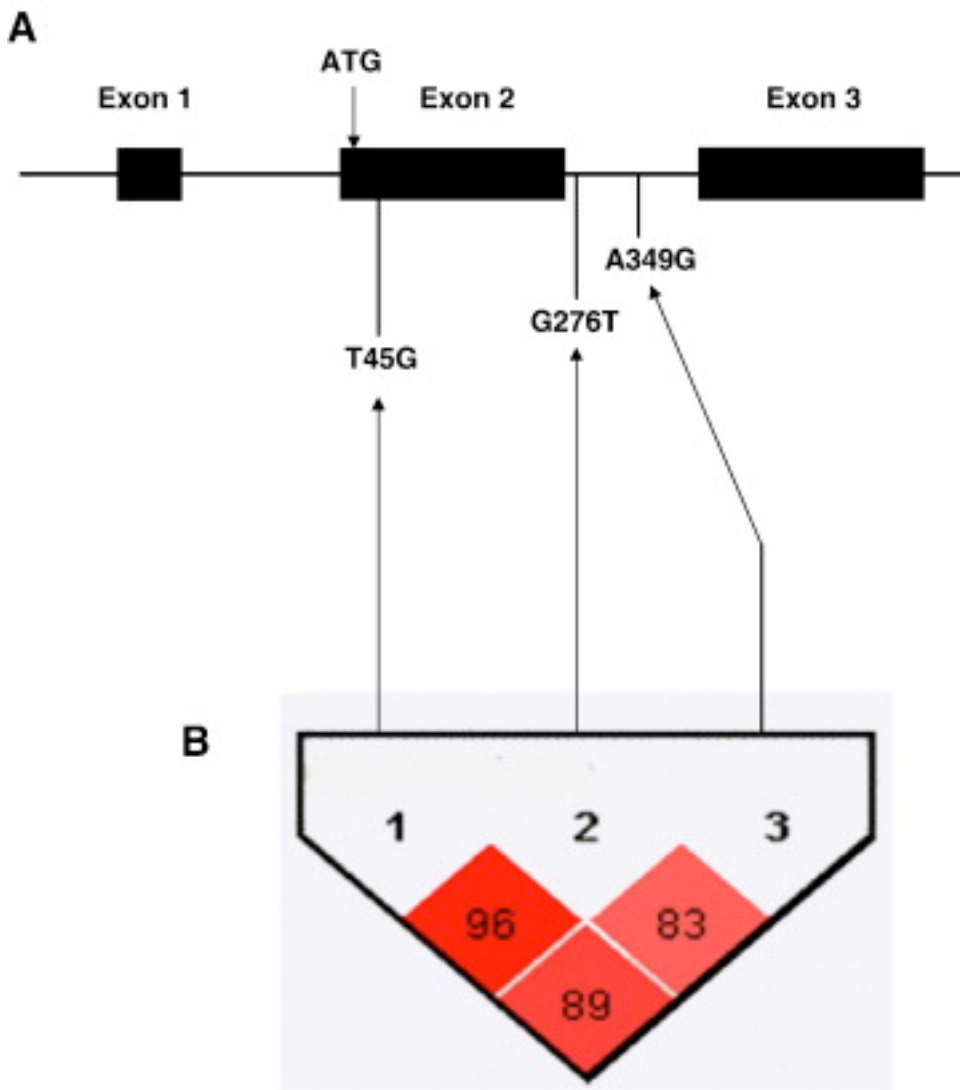
- We now know how to assess the null hypothesis as to whether a polymorphism has a causal effect on our phenotype
- Occasionally we will assess this hypothesis for a single genotype
- In quantitative genomics, we generally do not know the location of causal polymorphisms in the genome
- We therefore perform a hypothesis test of *many genotypes throughout the genome*
- This is a genome-wide association study (GWAS)

Quantitative genomic analysis II

- Analysis in a GWAS raises (at least) two issues we have not yet encountered:
  - An analysis will consist of many hypothesis tests (not just one)
  - We often do not test the causal polymorphism (usually)
- Note that this latter issue is a bit strange (!?) - how do we assess causal polymorphisms if we have not measured the causal polymorphism?
- Also note that causal genotypes will begin to be measured in our GWAS with next-generation sequencing data (but the issue will still be present!)

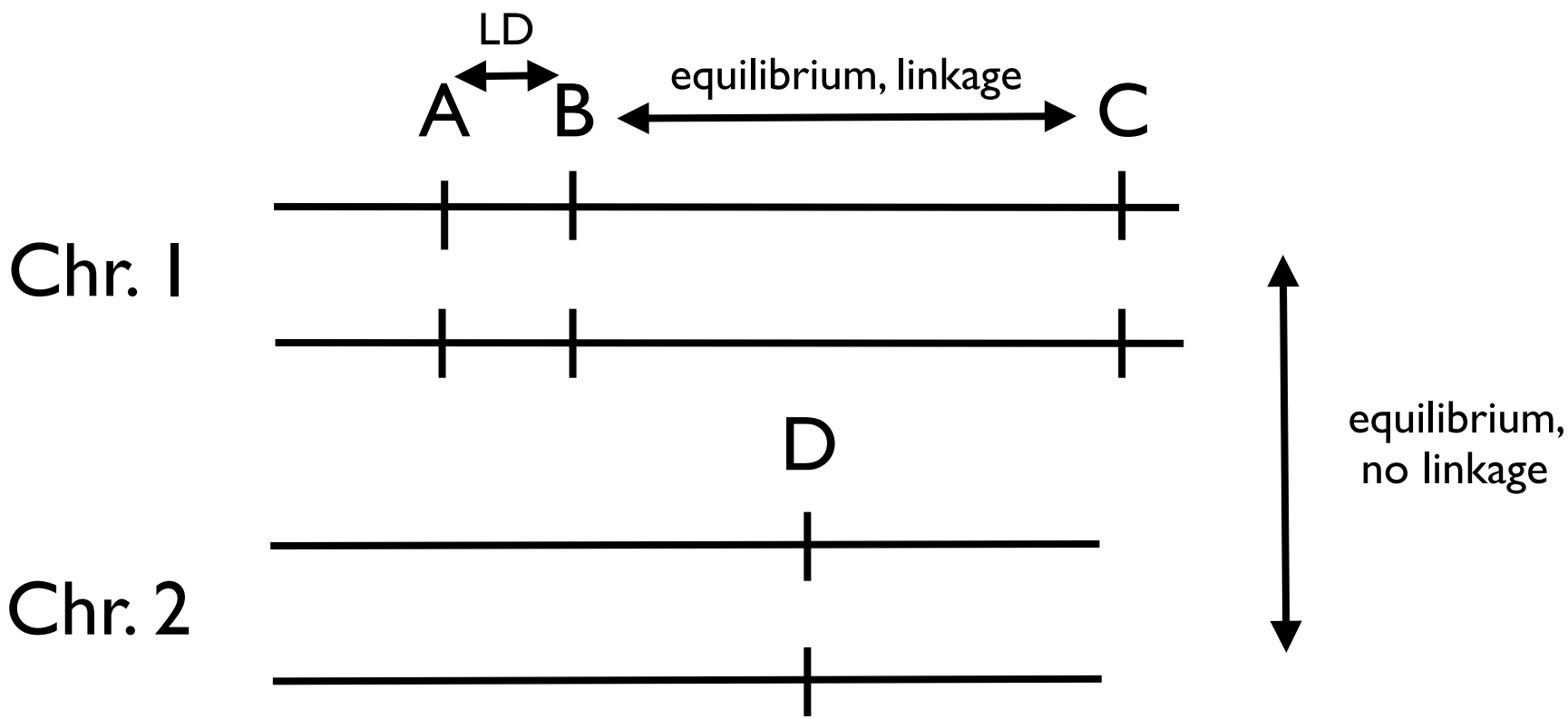
Correlation among genotypes

- If we test a (non-causal) genotype that is correlated with the causal genotype AND if correlated genotypes are in the same position in the genome THEN we can identify the genomic position of the casual genotype (!!)
- This is the case in genetic systems (why!?)
- Do we know which genotype is causal in this scenario?



Linkage Disequilibrium

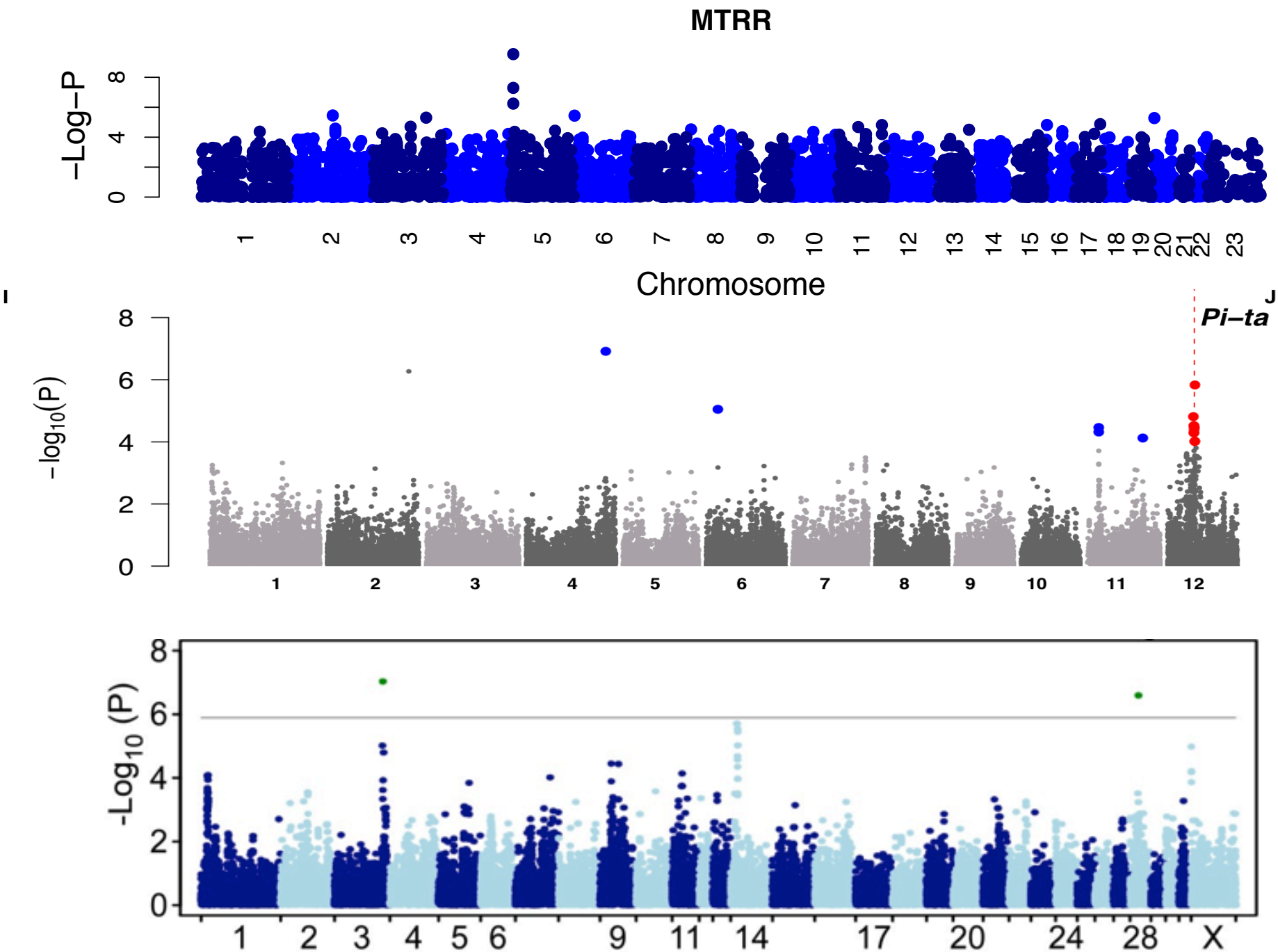
- Mapping the position of a causal polymorphism in a GWAS requires there to be LD for genotypes that are both physically linked and close to each other AND that markers that are either far apart or on different chromosomes to be in equilibrium
- Note that dis*equilibrium* includes both *linkage disequilibrium* AND other types of dis*equilibrium* (!!), e.g. gametic phase disequilibrium



Genome-Wide Association Study (GWAS)

- For a typical GWAS, we have a phenotype of interest and we do not know any causal polymorphisms (loci) that affect this phenotype (but we would like to find them!)
- In an "ideal" GWAS experiment, we measure the phenotype and *N* genotypes THROUGHOUT the genome for *n* independent individuals
- To analyze a GWAS, we perform *N* independent hypothesis tests
- When we reject the null hypothesis, we assume that we have located a position in the genome that contains a causal polymorphism (not the causal polymorphism!), hence a GWAS is a *mapping* experiment
- This is as far as we can go with a GWAS (!!) such that (often) identifying the causal polymorphism requires additional data and or follow-up experiments, i.e. GWAS is a starting point

The Manhattan plot: examples



That's it for today

- Next lecture (Thurs, March 14), we will continue our discussion of GWAS!