

## Lecture 2: Genetic Association Testing with Quantitative Traits

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## Introduction to Quantitative Trait Mapping

- ▶ In the previous session, we gave an overview of association testing methods when the trait of interest is binary (e.g. 1/0, affected/unaffected, dead/alive),
- ▶ Phenotypes of interest are often quantitative, and in this session we focus on the topic of genetic association testing with quantitative traits.
- ▶ The field of **quantitative genetics** is the study of the inheritance of continuously measured traits and their mechanisms.
- ▶ Vast amounts of literature on this topic!

## Introduction to Quantitative Trait Mapping

- ▶ Quantitative trait loci (QTL) mapping involves identifying genetic loci that influence the phenotypic variation of a quantitative trait.
- ▶ QTL mapping is commonly conducted with GWAS using common variants, such as variants with minor allele frequencies  $\geq 1\% - 5\%$
- ▶ There generally is no simple Mendelian basis for variation of quantitative traits
- ▶ Some quantitative traits can be largely influenced by a single gene as well as by environmental factors

## Introduction to Quantitative Trait Mapping

- ▶ Influences on a quantitative trait can also be due to a number of genes with similar (or differing) effects
- ▶ Many quantitative traits of interest are complex where phenotypic variation is due to a combination of both multiple genes and environmental factors
- ▶ Examples: Blood pressure, cholesterol levels, IQ, height, weight, etc.

## Quantitative Genetic Model

- ▶ The classical quantitative genetics model introduced by Ronald Fisher (1918) is  $Y = G + E$ , where  $Y$  is the phenotypic value,  $G$  is the genetic value, and  $E$  is the environmental deviation.
- ▶  $G$  is the combination of all genetic loci that influence the phenotypic value and  $E$  consists of all non-genetic factors that influence the phenotype
- ▶ The mean environmental deviation  $E$  is generally taken to be 0 so that the mean genotypic value is equal to the mean phenotypic value, i.e.,  $E(Y) = E(G)$

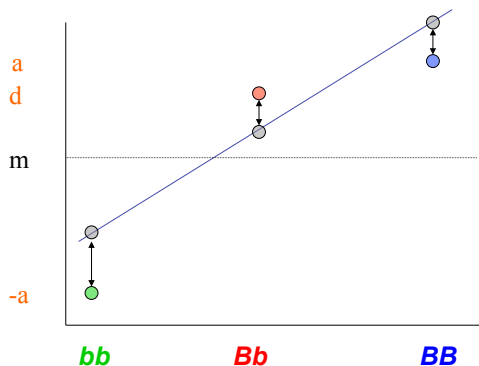
## Quantitative Genetic Model

- ▶ Consider a single locus. Fisher modeled the genotypic value  $G$  with a linear regression model (least squares) where the genotypic value can be partitioned into an additive component ( $A$ ) and deviations from additivity as a result of dominance ( $D$ ), where

$$G = A + D$$

# Linear Regression Model for Genetic Values

## Falconer model for single biallelic QTL



$$\begin{aligned} \text{Var}(X) &= \text{Regression Variance} + \text{Residual Variance} \\ &= \text{Additive Variance} + \text{Dominance Variance} \end{aligned}$$

## Components of Genetic Variance

- ▶ From the properties of least squares, the residuals are orthogonal to the fitted values, and thus  $Cov(A, D) = 0$ . So we have that

$$Var(G) = Var(A) + Var(D)$$

or

$$\sigma_G^2 = \sigma_A^2 + \sigma_D^2$$

- ▶  $\sigma_A^2$  is the **additive genetic variance**. It is the genetic variance associated with the average additive effects of alleles
- ▶  $\sigma_D^2$  is the **dominance genetic variance**. It is the genetic variance associated with the dominance effects.



## Heritability

- ▶ The heritability of a trait is written in terms of the components of variances of the trait.
- ▶ Remember that  $Y = G + E = A + D + E$
- ▶ The following ratio of variance components

$$h^2 = \frac{\sigma_A^2}{\sigma_Y^2}$$

is defined to be the **narrow-sense heritability** (or simply heritability)

- ▶  $h^2$  is the proportion of the total phenotypic variance that is due to additive effects.
- ▶ Heritability can also be viewed as the extent to which phenotypes are determined by the alleles transmitted from the parents.

# Heritability

- ▶ The **broad-sense heritability** is defined to be

$$H^2 = \frac{\sigma_G^2}{\sigma_Y^2}$$

- ▶  $H^2$  is the proportion of the total phenotypic variance that is due to all genetic effects (additive and dominance)
- ▶ There are a number of methods for heritability estimation of a trait.

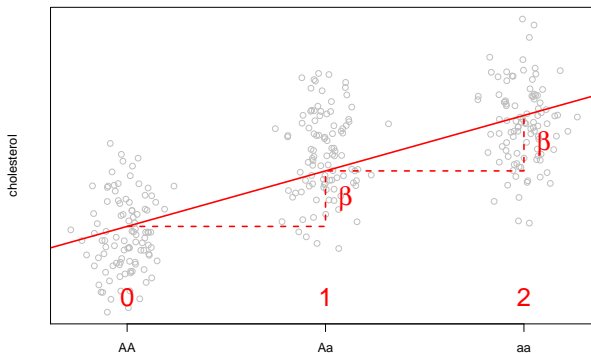
## QTL Mapping

- ▶ For traits that are heritable, i.e., traits with a non-negligible genetic component that contributes to phenotypic variability, identifying (or mapping) QLT that influence the trait is often of interest.
- ▶ Linear regression models are commonly used for QTL mapping
- ▶ Linear regression models will often include a single genetic marker (e.g., a SNP) as predictor in the model, in addition to other relevant covariates (such as age, sex, etc.), with the quantitative phenotype as the response

## Linear regression with SNPs

Many analyses fit the 'additive model'

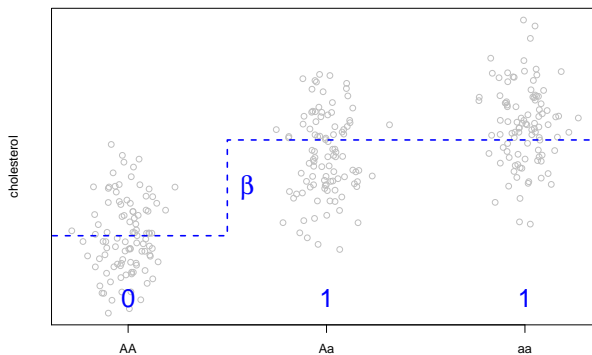
$$y = \beta_0 + \beta \times \# \text{minor alleles}$$



## Linear regression, with SNPs

An alternative is the 'dominant model';

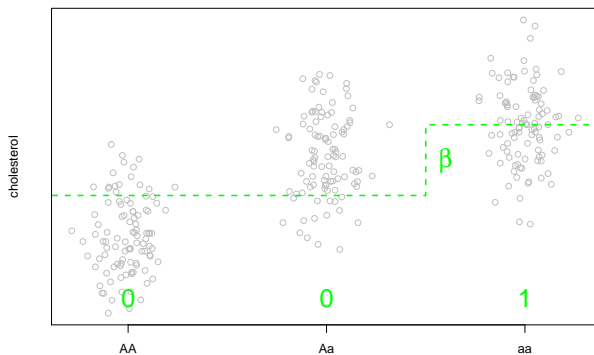
$$y = \beta_0 + \beta \times (G \neq AA)$$



# Linear regression, with SNPs

or the 'recessive model';

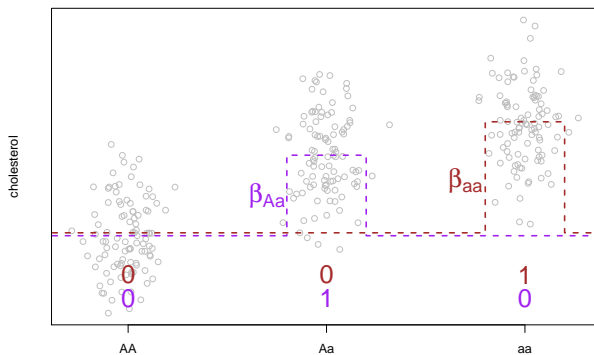
$$y = \beta_0 + \beta \times (G == aa)$$



## Linear regression, with SNPs

Finally, the 'two degrees of freedom model';

$$y = \beta_0 + \beta_{Aa} \times (G == Aa) + \beta_{aa} \times (G == aa)$$

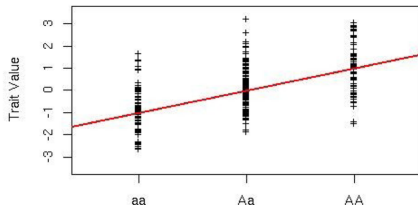


## Additive Genetic Model

- ▶ Most GWAS perform single SNP association testing with linear regression assuming an additive model.

### Unrelated Samples

$$\hat{y}_i = \mu + \hat{\beta}x_i$$





## Additive Genetic Model

- ▶ The additive linear regression model also has a nice interpretation, as we saw from Fisher's classical quantitative trait model!
- ▶ The coefficient of determination ( $r^2$ ) of an additive linear regression model gives an estimate of the proportion of phenotypic variation that is explained by the SNP (or SNPs) in the model, e.g., the "SNP heritability"

## Additive Genetic Model

- ▶ Consider the following additive model for association testing with a quantitative trait and a SNP with alleles  $A$  and  $a$ :

$$Y = \beta_0 + \beta_1 X + \epsilon$$

where  $X$  is the number of copies of the reference allele  $A$ .

- ▶ What would your interpretation of  $\epsilon$  be for this particular model?

## Association Testing with Additive Model

$$Y = \beta_0 + \beta_1 X + \epsilon$$

- ▶ Two test statistics for  $H_0 : \beta_1 = 0$  versus  $H_a : \beta_1 \neq 0$

$$T = \frac{\hat{\beta}_1}{\sqrt{\text{var}(\hat{\beta}_1)}} \sim \mathbf{t}_{N-2} \approx N(0, 1) \text{ for large } N$$

$$T^2 = \frac{\hat{\beta}_1^2}{\text{var}(\hat{\beta}_1)} \sim \mathbf{F}_{1, N-2} \approx \chi_1^2 \text{ for large } N$$

where

$$\text{var}(\hat{\beta}_1) = \frac{\sigma_\epsilon^2}{S_{XX}}$$

and  $S_{XX}$  is the corrected sum of squares for the  $X_i$ 's

## Statistical Power for Detecting QTL

$$Y = \beta_0 + \beta_1 X + \epsilon$$

- ▶ We can also calculate the power for detecting a QTL for a given effect size  $\beta_1$  for a SNP.
- ▶ For simplicity, assume that  $Y$  has been standardized so that with  $\sigma_Y^2 = 1$ .
- ▶ Let  $p$  be the frequency of the  $A$  allele in the population

$$\sigma_Y^2 = \beta_1^2 \sigma_X^2 + \sigma_\epsilon^2 = 2p(1-p)\beta_1^2 + \sigma_\epsilon^2$$

- ▶ Let  $h_s^2 = 2p(1-p)\beta_1^2$ , so we have  $\sigma_Y^2 = h_s^2 + \sigma_\epsilon^2$
- ▶ Interpret  $h_s^2$  (note that we assume that trait is standardized such that  $\sigma_Y^2 = 1$ )

## Statistical Power for Detecting QTL

- ▶ Also note that  $\sigma_\epsilon^2 = 1 - h_s^2$ , so we can write  $\text{Var}(\hat{\beta}_1)$  as the following:

$$\text{var}(\hat{\beta}_1) = \frac{\sigma_\epsilon^2}{S_{XX}} \approx \frac{\sigma_\epsilon^2}{N(2p(1-p))} = \frac{1 - h_s^2}{2Np(1-p)}$$

- ▶ To calculate power of the test statistic  $T^2$  for a given sample size  $N$ , we need to first obtain the expected value of the non-centrality parameter  $\lambda$  of the chi-squared ( $\chi^2$ ) distribution which is the expected value of the test statistic  $T$  squared:

$$\lambda = [E(T)]^2 \approx \frac{\beta_1^2}{\text{var}(\hat{\beta}_1)} = \frac{Nh_s^2}{1 - h_s^2}$$

since  $h_s^2 = 2p(1-p)\beta_1^2$

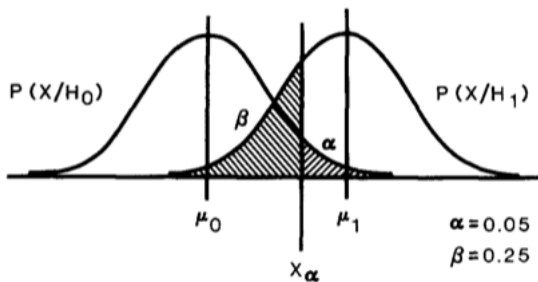
## Required Sample Size for Power

- ▶ Can also obtain the required sample size given type-I error  $\alpha$  and power  $1 - \beta$ , where the type-II error is  $\beta$  :

$$N = \frac{1 - h_s^2}{h_s^2} (z_{(1-\alpha/2)} + z_{(1-\beta)})^2$$

where  $z_{(1-\alpha/2)}$  and  $z_{(1-\beta)}$  are the  $(1 - \alpha/2)$ th and  $(1 - \beta)$ th quantiles, respectively, for the standard normal distribution.

## Statistical Power for Detecting QTL



# Genetic Power Calculator (PGC)

<http://pngu.mgh.harvard.edu/~purcell/gpc/>

Genetic Power Calculator



## Genetic Power Calculator

S. Purcell & P. Sham, 2001-2009

This site provides automated power analysis for variance components (VC) quantitative trait locus (QTL) linkage and association tests in sibships, and other common tests. Suggestions, comments, etc to [Sham Purcell](#).

If you use this site, please reference the following [Bioinformatics article](#):

Purcell S, Cherny SS, Sham PC. (2003) Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics*, 19(1):149-150.

### Modules

<a href="#">Case-control for discrete traits</a>	<a href="#">Notes</a>
<a href="#">Case-control for threshold-selected quantitative traits</a>	<a href="#">Notes</a>
<a href="#">QTL association for sibships and singletons</a>	<a href="#">Notes</a>
<a href="#">TDT for discrete traits</a>	<a href="#">Notes</a>
<a href="#">TDT and parentTDT with ascertainment</a>	<a href="#">Notes</a>
<a href="#">TDT for threshold-selected quantitative traits</a>	<a href="#">Notes</a>
<a href="#">Epistasis power calculator</a>	<a href="#">Notes</a>
<a href="#">QTL linkage for sibships</a>	<a href="#">Notes</a>
<a href="#">Probability Function Calculator</a>	<a href="#">Notes</a>

## Genetic Power Calculator

### QTL Association for Sibships

Total QTL variance :  (0 - 1)  
 Dominance : additive QTL effects :  (0 - 1)  No dominance (\* see below)  
 QTL increaser allele frequency :  (0 - 1)  
 Marker M1 allele frequency :  (0 - 1)  
 Linkage disequilibrium (D-prime) :  (0 - 1)  
 Sibling correlation :  (0 - 1) (\* see below)

Sample Size :  (0 - 10000000) (N=families, not individuals)  
 Sibship Size :   Both parents genotyped

User-defined type I error rate :  (0.00000001 - 0.5)  
 User-defined power: determine N :  (0 - 1)  
 (1 - type II error rate)



## Missing Heritability

Disease	Number of loci	Percent of Heritability Measure Explained	Heritability Measure
Age-related macular degeneration	5	50%	Sibling recurrence risk
Crohn's disease	32	20%	Genetic risk (liability)
Systemic lupus erythematosus	6	15%	Sibling recurrence risk
Type 2 diabetes	18	6%	Sibling recurrence risk
HDL cholesterol	7	5.2%	Phenotypic variance
Height	40	5%	Phenotypic variance
Early onset myocardial infarction	9	2.8%	Phenotypic variance
Fasting glucose	4	1.5%	Phenotypic variance

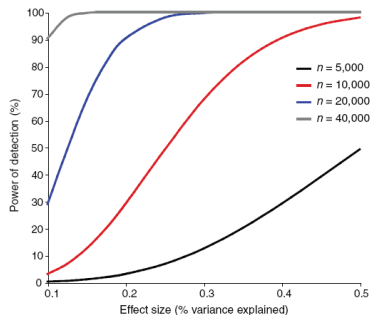
- GWAS works
- Effect sizes are typically small
  - Disease: OR  $\sim 1.1$  to  $\sim 1.3$
  - Quantitative traits: % var explained  $\ll 1\%$



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NATURE 422 (2002)

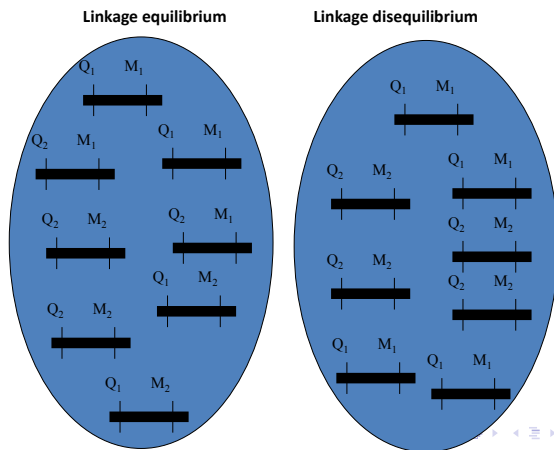
## Genetic Power Calculator (Shaun Purcell)

<http://pngu.mgh.harvard.edu/~purcell/gpc/>

**Figure 1** Statistical power of detection in GWAS for variants that explain 0.1–0.5% of the variation at a type I error rate of  $5 \times 10^{-7}$  (calculated using the Genetic Power Calculator<sup>15</sup>). Shown is the power to detect a variant with a given effect size, assuming this type I error rate, which is typical for a GWAS with a sample size of  $n = 5,000$ – $40,000$ .

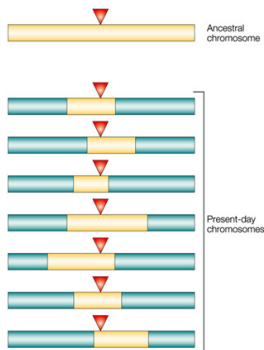
## LD Mapping of QTL

- ▶ For GWAS, the QTL generally will not be genotyped in a study



## LD Mapping of QTL

# Linkage disequilibrium around an ancestral mutation



## LD Mapping of QTL

- ▶  $r^2$  = LD correlation between QTL and genotyped SNP
- ▶ Proportion of variance of the trait explained at a SNP  $\approx r^2 h_s^2$
- ▶ Required sample size for detection is

$$N \approx \frac{1 - r^2 h_s^2}{r^2 h_s^2} (z_{(1-\alpha/2)} + z_{(1-\beta)})^2$$

- ▶ Power of LD mapping depends on the experimental sample size, variance explained by the causal variant and LD with a genotyped SNP