An Introduction to Quantitative Genetics: Using the Single Locus Model to Understand the Foundations of Genome-Wide Association and Genomic Selection

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Introductory plant breeding course

Section on quantitative genetics

- Basics of quantitve traits and selection
- Approx. 1/3 of course

Expectations from students at this point

- Understand basics of Mendelian inheritance
- Familar terms
    - gene
    - allele
    - dominance

Introduction

Quatitative genetics is statistical language

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- Population parameters are *estimated* from a sample of the population
    - Allele and genotypic frequencies
    - Gene "effects"
    - Means and variances

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- Population parameters are *estimated* from a sample of the population
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    - Gene "effects"
    - Means and variances

What does this language describe?

- Inheritance of traits, continuous and discrete
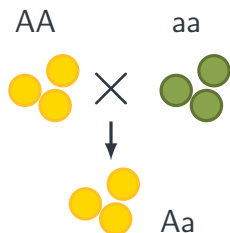- Changes of a population through time

Gregor Mendel
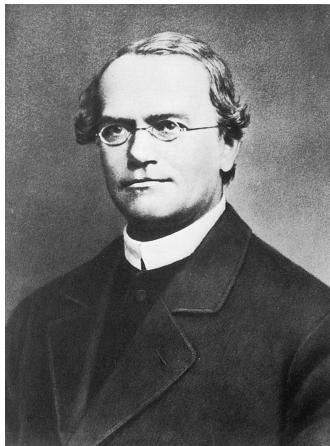
Experiments in Plant Hybridization (1866)

- Single gene inheritance
- Qualitative traits
- "Complete" Dominance
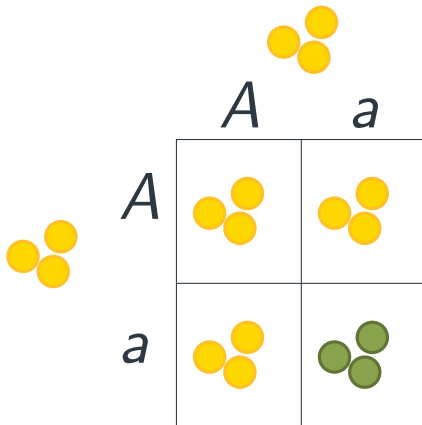- Independent assortment

Lost for 34 years, rediscovered in 1900
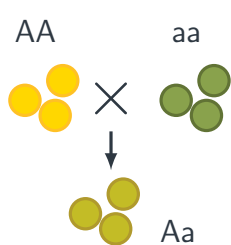
"Complete" Dominance

AA   aa

Aa

Mendel observed some
traits were "hidden"

- reappeared when
  recombined

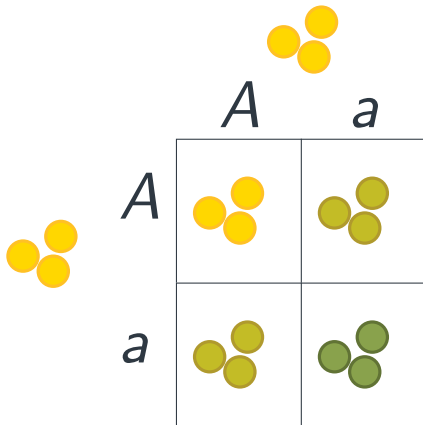- inheritance of factors,
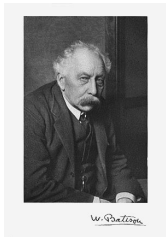 i.e. "genes"

"Incomplete" Dominance

Not true for all traits
- some seemed to blend
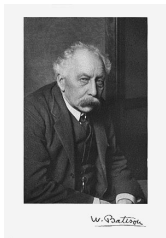
Two waring sides

Mendelians

William Bateson

Biometricians

Karl Pearson

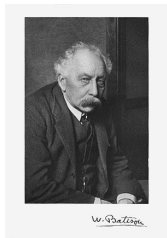# Two waring sides

Mendelians

Quantitative Genetics
is born

Biometricians

William Bateson

Ronald Fisher

Karl Pearson

Two waring sides

Mendelians

Quantitative Genetics
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Biometricians

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- 1918. The Correlation between Relatives on the Supposition of Mendelian Inheritance
- Used Mendelian genetics to explain continuous variation

Qualitative vs Quantitative traits

- Qualitative traits
  - yellow / green
  - tall / short
  - early / late
  - high / low yielding

- Quantitative traits
  - chlorophyll (g)
  - plant height (cm)
  - days to flowering
  - bushels acre^{-1}

We will treat the genetics of continuous traits as a (linear) mathematical problem!

Additive Single Locus

Additive effects increase linearly with the total number of alleles
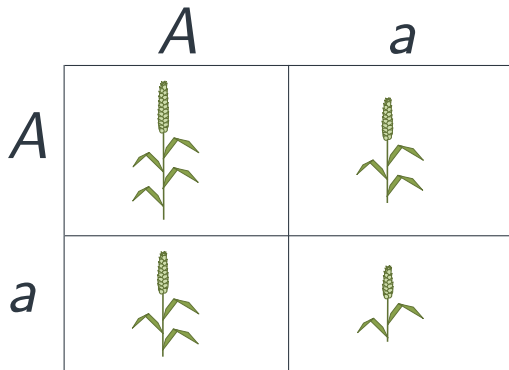
The Single Locus Model

Phenotype = Genotype + Environment

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$$y_{ij} = G_i + e_{ij}$$

- Genotype $= G_i =$ genetic effect of the ith individual
- residual $= e_{ij} =$ some deviation from the genetic effect

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We will begin with the assumption that only one locus effects our phenotype

The Single Locus Model II - Matrix notation

$= AA$

$= Aa$

$= aa$

The Single Locus Model II - Matrix notation

$= AA$ $\qquad\qquad y_1 = x_1\beta_a + e_1$

$= Aa$ $\qquad\qquad y_2 = x_2\beta_a + e_2$

$= aa$ $\qquad\qquad y_3 = x_3\beta_a + e_3$

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$$\mathbf{y} = \mathbf{x}_a\beta_a + \mathbf{e}$$

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} aa \\ Aa \\ Aa \\ \vdots \\ AA \end{bmatrix} \begin{bmatrix} \beta_a \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ \vdots \\ e_n \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \\ 1 \\ \vdots \\ 2 \end{bmatrix} \begin{bmatrix} \beta_a \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ \vdots \\ e_n \end{bmatrix}$$

The Single Locus Model III - Dominance

$$\mathbf{y} = \mathbf{x}_a \beta_a + \mathbf{x}_d \beta_d + \mathbf{e}$$

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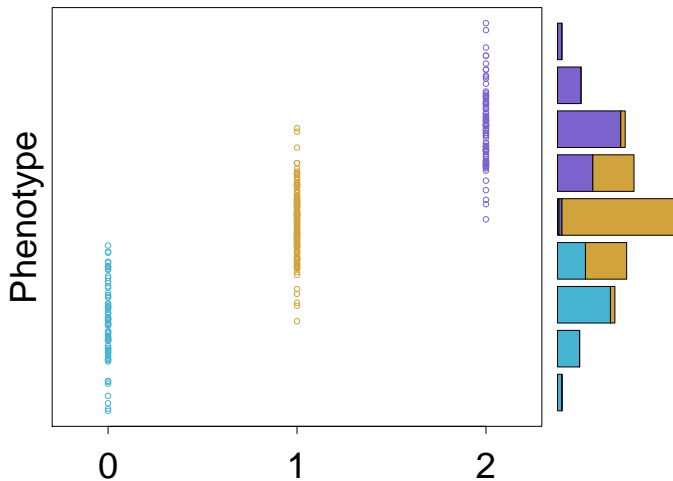
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\begin{bmatrix} \beta_a \\ \beta_d \end{bmatrix}
+
\begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ \vdots \\ e_n \end{bmatrix}
=
\begin{bmatrix} 0 & 0 \\ 1 & 1 \\ 1 & 1 \\ \vdots & \vdots \\ 2 & 0 \end{bmatrix}
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Lets see how this works...

Additive only
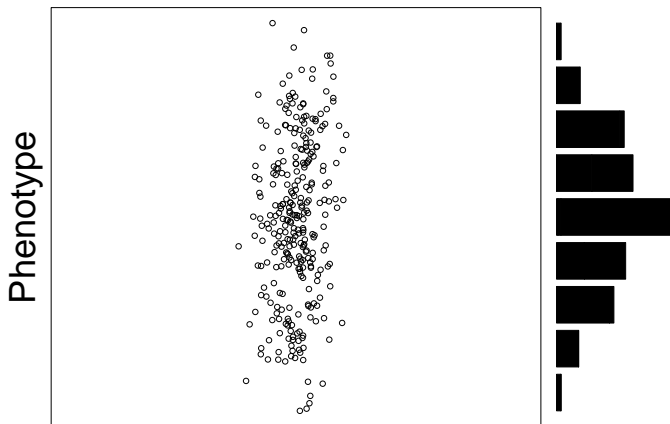
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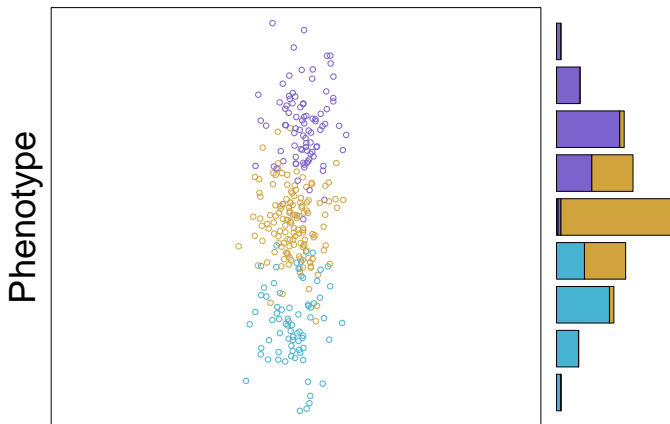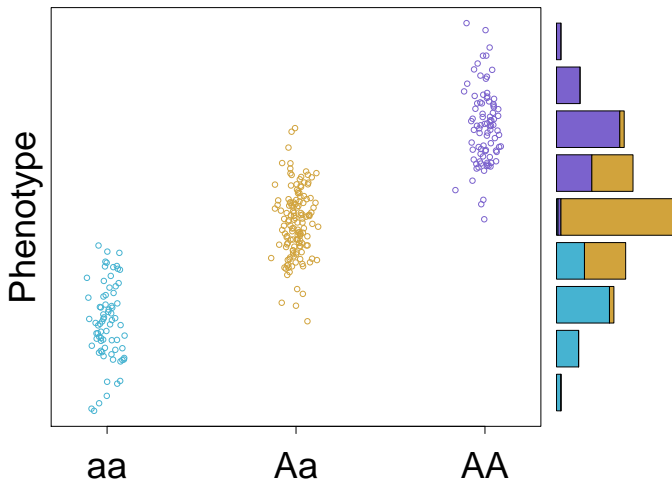
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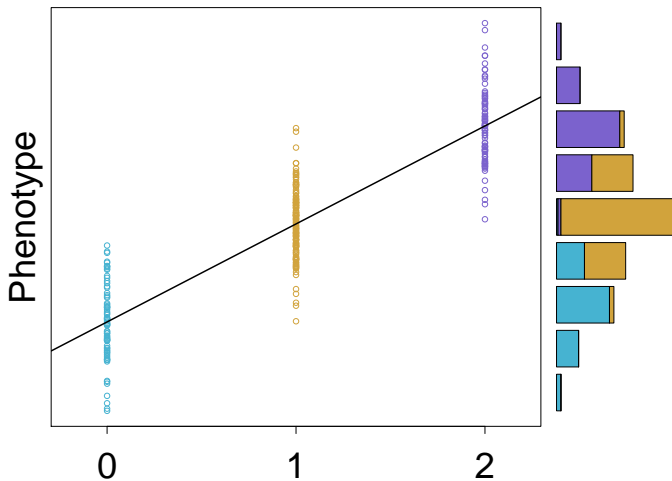
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Additive with Dominance
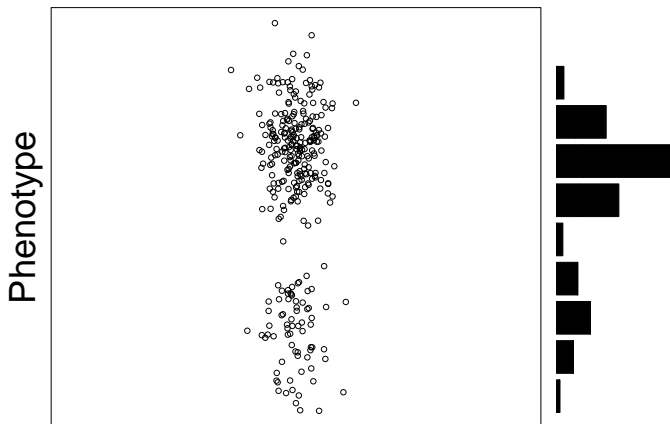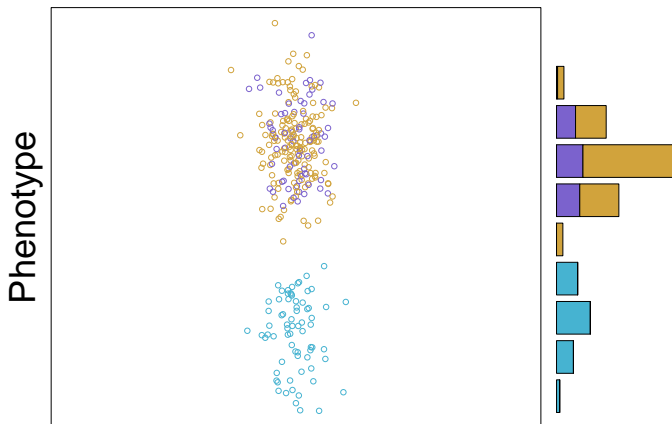
Additive with Dominance
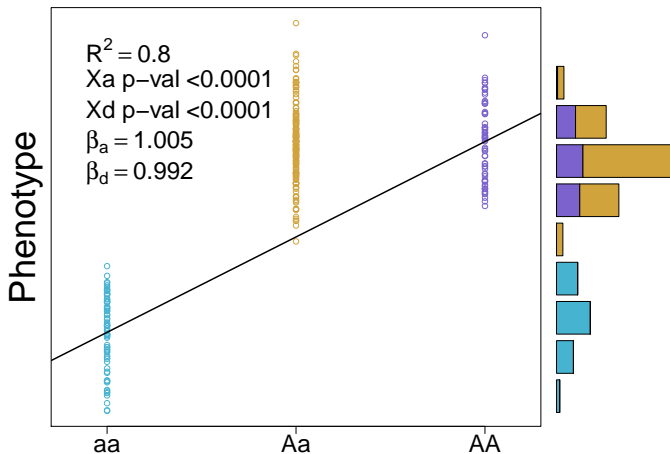
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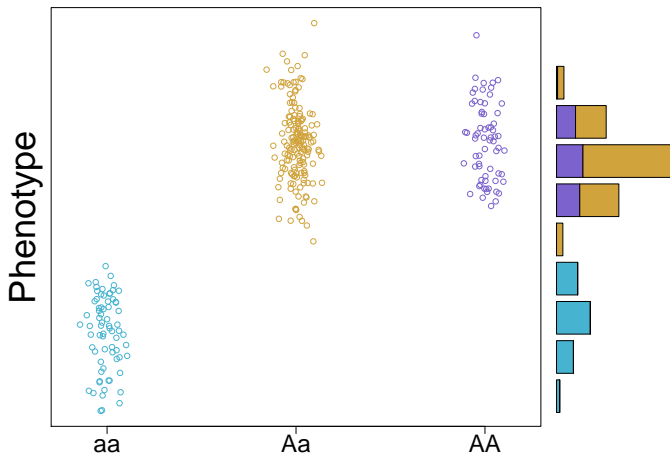
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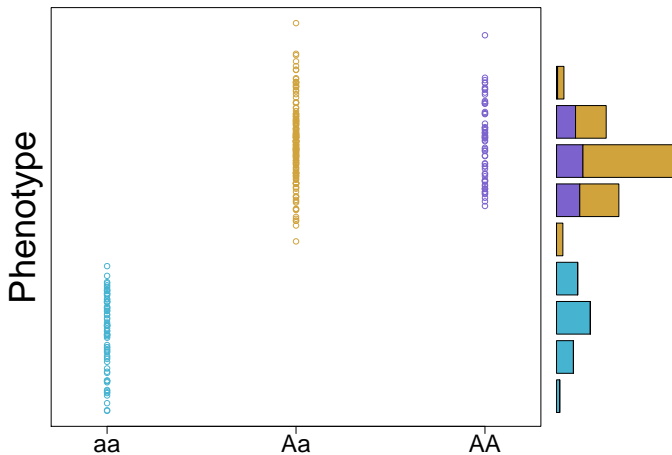
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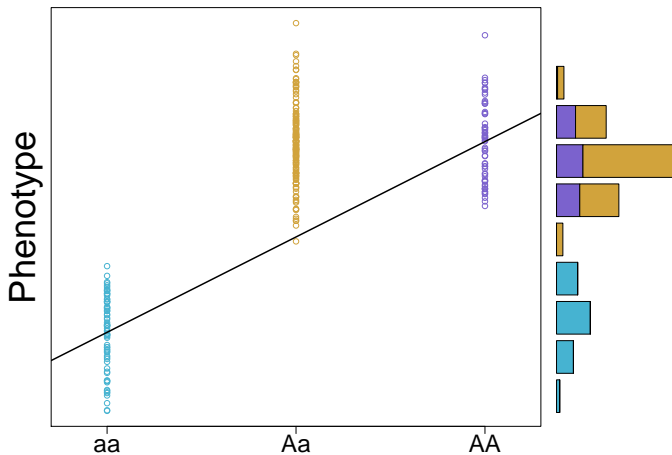
Additive with Dominance

Lets simulate it

Let's start with the single locus:
nsantantonio.shinyapps.io/singlelocus/

Genetic Variance

Let n = number of individuals
Let P = frequency of AA's
Let 2Q = frequency of Aa's   such that $P + 2Q + R = 1$
Let R = frequency of aa's

$$E[\mathbf{x}] = \frac{1}{n} \sum_{i=1} x_i$$
$$\mu = Pa + 2Qd - Ra$$

$$Var(\mathbf{x}) = \frac{1}{n} \sum_{i=1} (x_i - \mu)^2$$
$$= P(a - \mu)^2 + 2Q(d - \mu)^2 - R(a - \mu)^2$$

Genetic Variance

Breeder's Equation:

$$\Delta_R = \frac{ir\sigma_a}{c}$$

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Effect of allele frequency on genetic variance
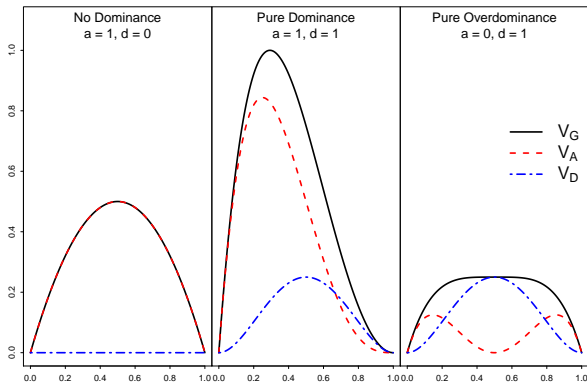
Finding causal genes

How do we find causal genes / variants?

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DNA markers!

- genotype individuals with genome-wide markers
- statistical association between marker and trait
    - $H_0 : \beta_a = 0$ and $\beta_d = 0$
    - $H_0 : \beta_a \neq 0$ or $\beta_d \neq 0$

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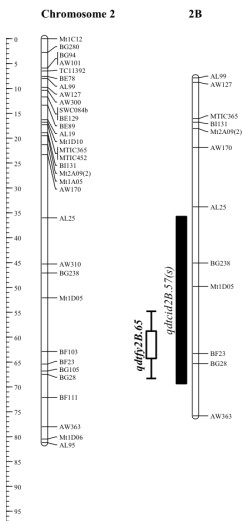
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Bi-parental mapping populations

- maximize allele frequencies
  - Statistical power

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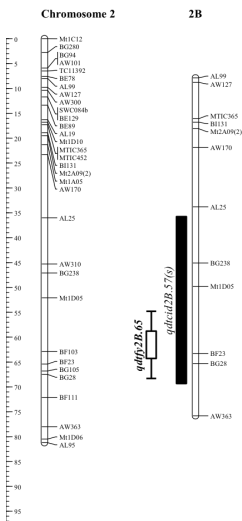
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Bi-parental mapping populations

- maximize allele frequencies

  - Statistical power

- maximize linkage

  - poor precision...

Genome-Wide Association Studies

Association Mapping Population
- Take advantage of historical recombination events (low linkage)

Genome-Wide Association Studies

Association Mapping Population
- Take advantage of historical recombination events (low linkage)
- However, more closely related individuals will share functional alleles, as well as *many* other alleles

Population Structure Problem
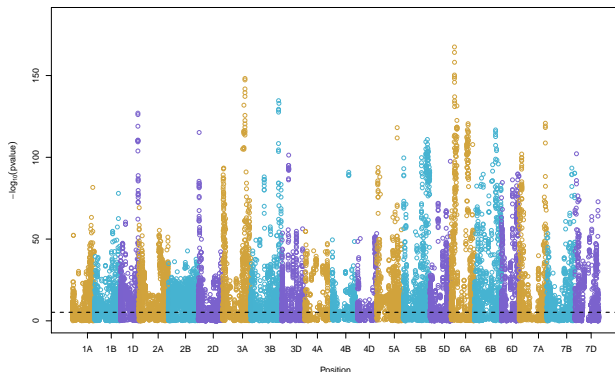
Population structure "inflates" significance. Correct with kinship.
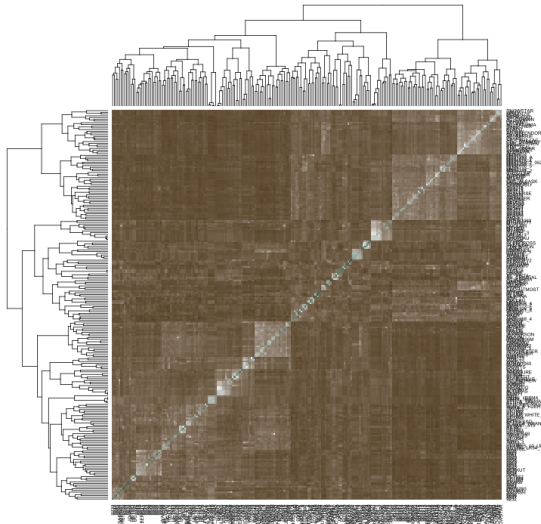
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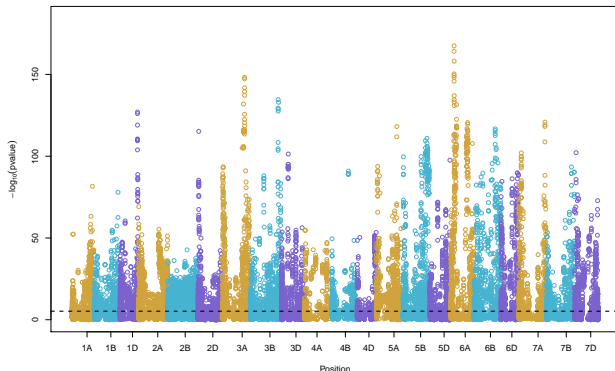
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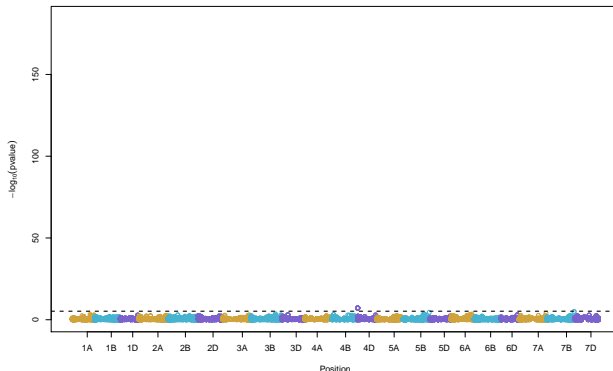
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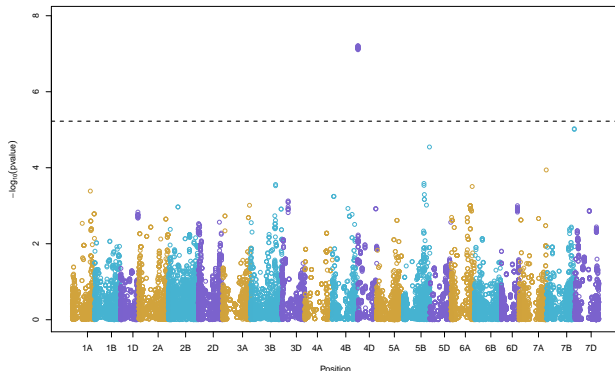
Finding causal genes

Population structure "inflates" significance.

Additive Two Loci

Lets see what happens when we have many loci

Let's start with the single locus:
nsantantonio.shinyapps.io/quantitative/

Genomic Prediction

$$G_i = \sum_{i=1}^{m} \mathbf{x}_{a_i} \beta_{a_i}$$

- Genetic value of an individual is the sum of its allele effects
- Interestingly, same as modeling kinship between individuals!

$$\mathbf{y} = \mathbf{1}\mu + \mathbf{X}\beta + \mathbf{Z}\mathbf{g} + \varepsilon$$
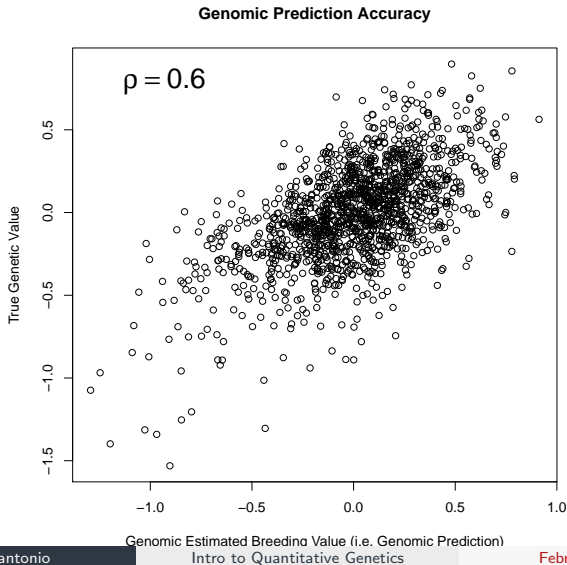
- $\mathbf{1}_n\mu$ is the global mean
- $\mathbf{X}$ is the design matrix
- β is the vector of fixed environmental effects.
- $\mathbf{Z}$ is the incidence matrix
- $\mathbf{g} \sim \mathcal{N}(0, \sigma_a^2 \mathbf{K})$, random genetic effects
- $\varepsilon \sim \mathcal{N}(0, \sigma^2 \mathbf{R})$, error

Mixed Model Equations

$$y = 1\mu + X\beta + Zg + \varepsilon$$

$$\begin{bmatrix} \hat{\beta} \\ \hat{g} \end{bmatrix} = \begin{bmatrix} X^\mathsf{T}R^{-1}X & X^\mathsf{T}R^{-1}Z \\ Z^\mathsf{T}R^{-1}X & Z^\mathsf{T}R^{-1}Z + A^{-1}\left(\frac{\sigma_e^2}{\sigma_g^2}\right) \end{bmatrix}^{-1} \begin{bmatrix} X^\mathsf{T}R^{-1}y \\ Z^\mathsf{T}R^{-1}y \end{bmatrix}$$

Genomic Prediction of Grain Yield

Genomic Prediction Accuracy

Genomic Selection

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