Genome 371, 8 March 2010, Lecture 15

Quantitative and Population Genetics

- What are quantitative traits and why do we care?
  - genetic basis of quantitative traits
  - heritability
- Basic concepts of population genetics

Final is Monday, March 15

8:30 a.m.

Hogness Auditorium - in Health Sciences
room A420

What Phenotypes/Diseases

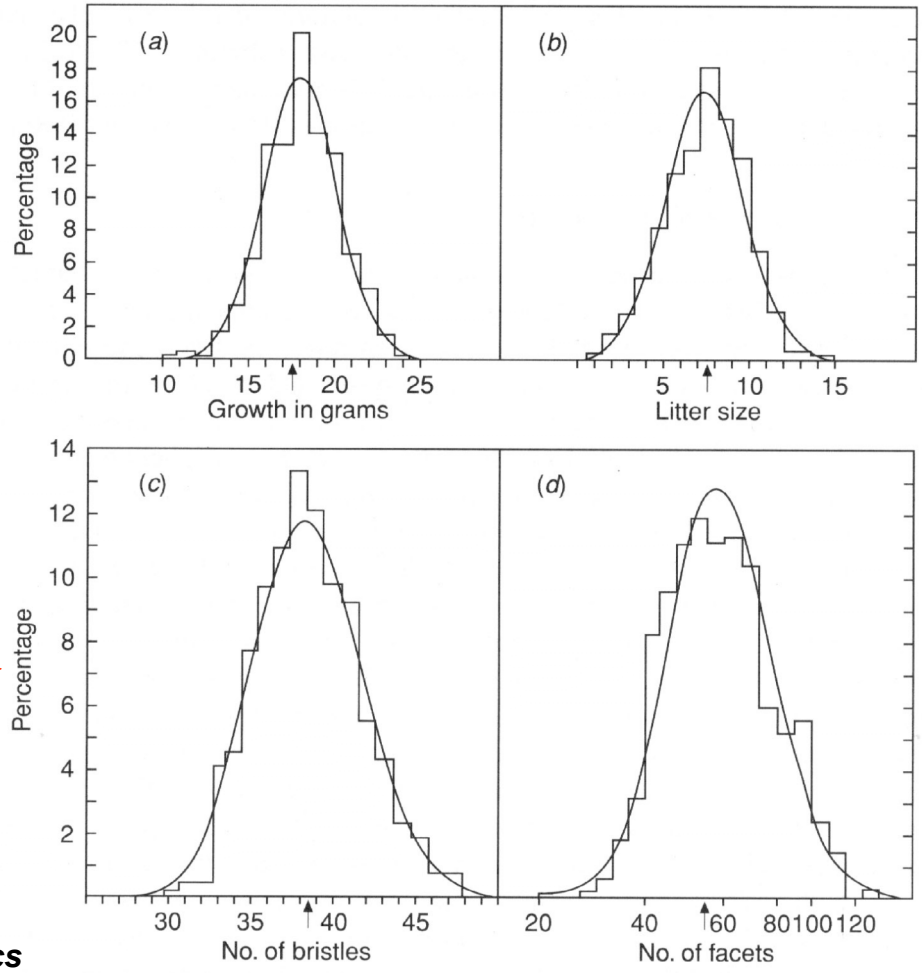
Do You Find Most Interesting?

Quantitative Genetics

- Concerned with the inheritance of differences between individuals that are a matter of degree rather than kind (i.e., quantitative not qualitative)

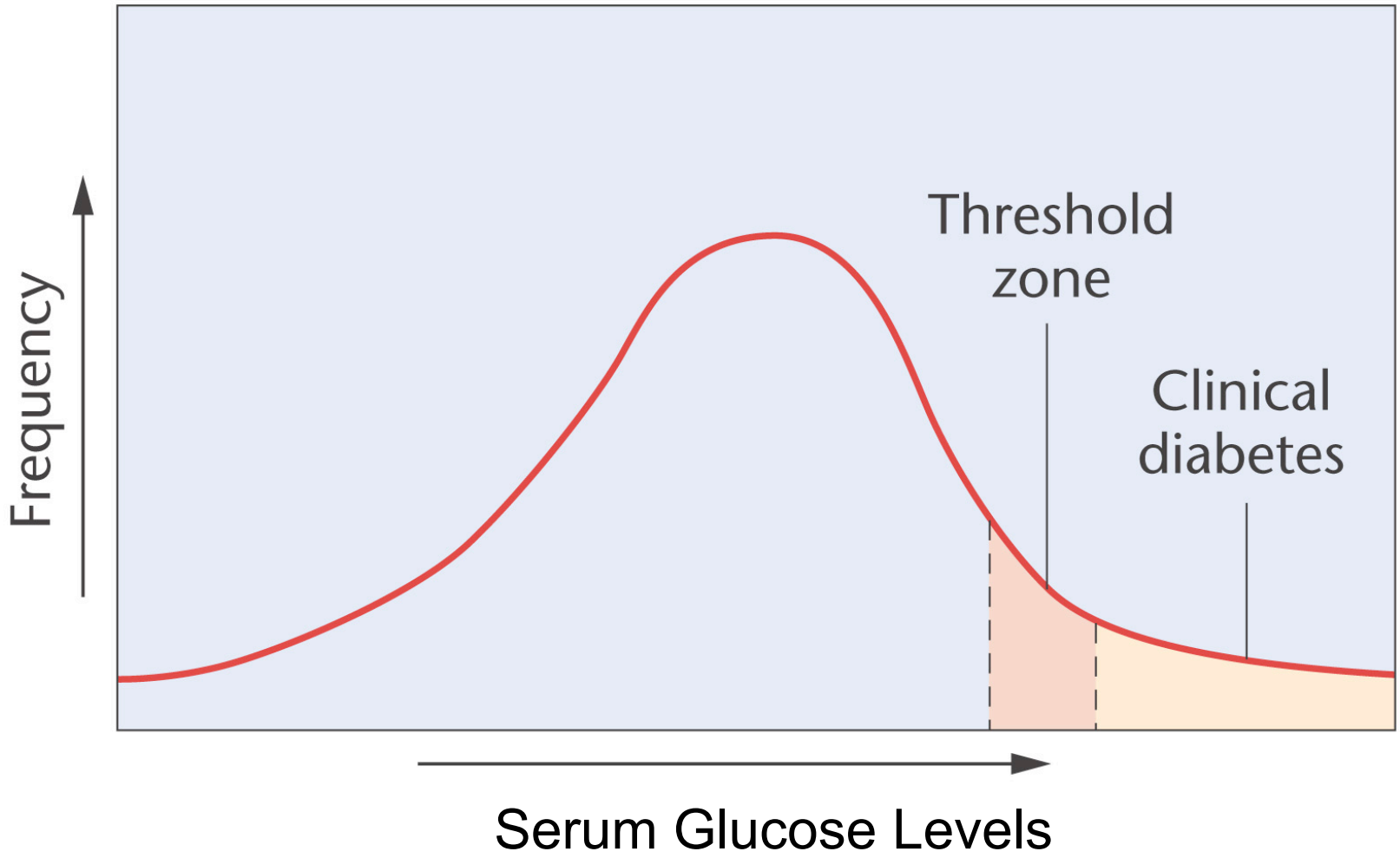
Mice →

Fruit Flies →



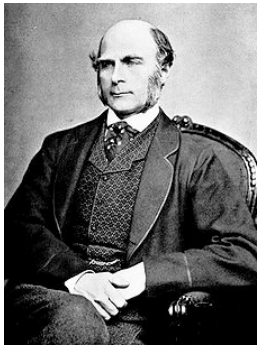
In:*Introduction to Quantitative Genetics*
Falconer & Mackay 1996

Many Discrete Traits Have an Underlying Quantitative Basis



Some Puzzling Aspects of Quantitative Traits

- Legendary debate in the early 1900's on the genetic basis of quantitative traits



-vs-

"Mendelian" "Biometrician"

- Genes are discrete and should lead to discrete phenotypes

R- r r

Sir Ronald Fisher To the Rescue

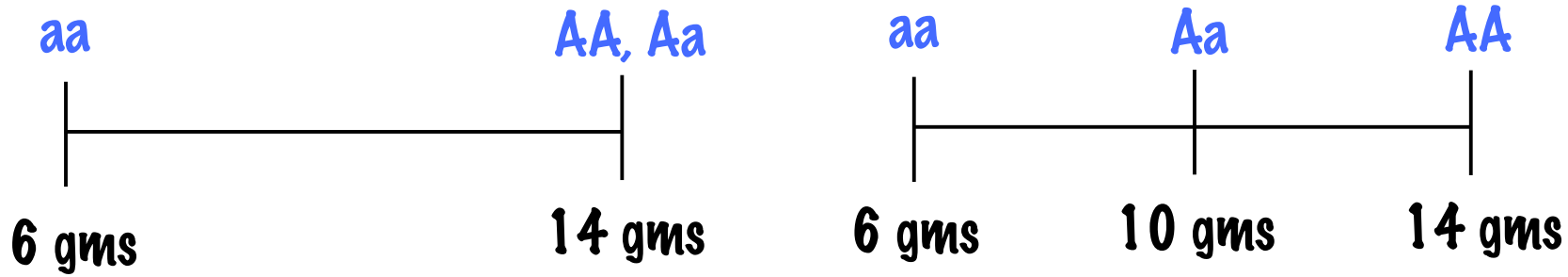
1918 paper "The Correlation Between Relatives on the Supposition of Mendelian Inheritance" reconciled this conflict

Showed that *inherently discontinuous variation* caused by genetic segregation is translated into the *continuous variation of quantitative characters*

Genetic Basis of Quantitative Traits

First, we need a model: single locus with alleles A and a

Familiar model	Additive model
one allele is dominant (uppercase)	Active allele (uppercase)
other allele is recessive (lowercase)	Inactive allele (lower case)



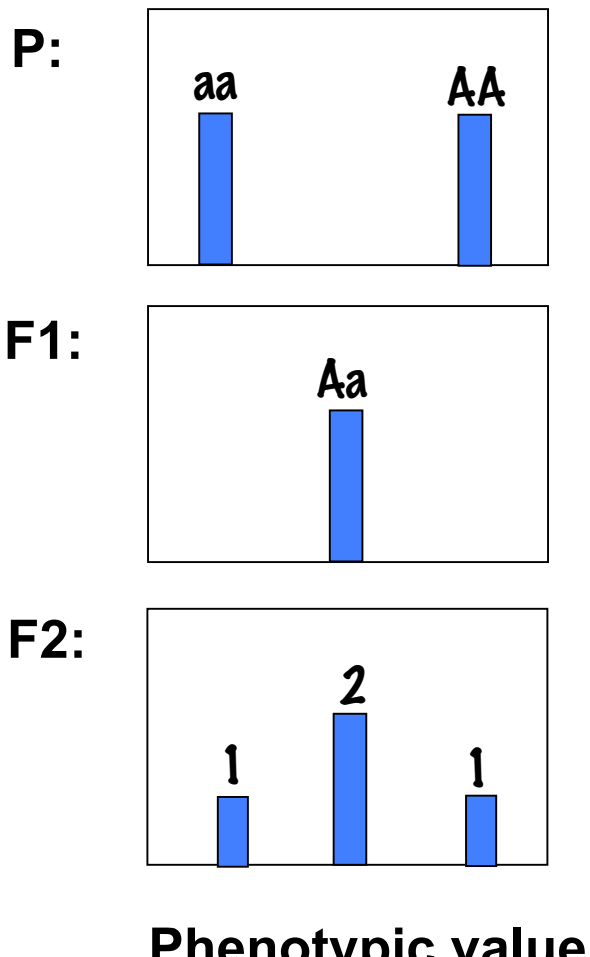
A General Additive Single Locus Model

If we do a Aa x Aa cross we would expect the following genotypes and phenotypes in the progeny:

Genotype	Number of active alleles	Frequency	Phenotypic value
AA	2	$^1/_4$	$\mu + 2x$
Aa	1	$^1/_2$	$\mu + x$
aa	0	$^1/_4$	μ

μ = average phenotype

Graphically…



What Happens With Two Genes?

If we do a AaBb x AaBb cross we would expect the following genotypes and phenotypes in the progeny:

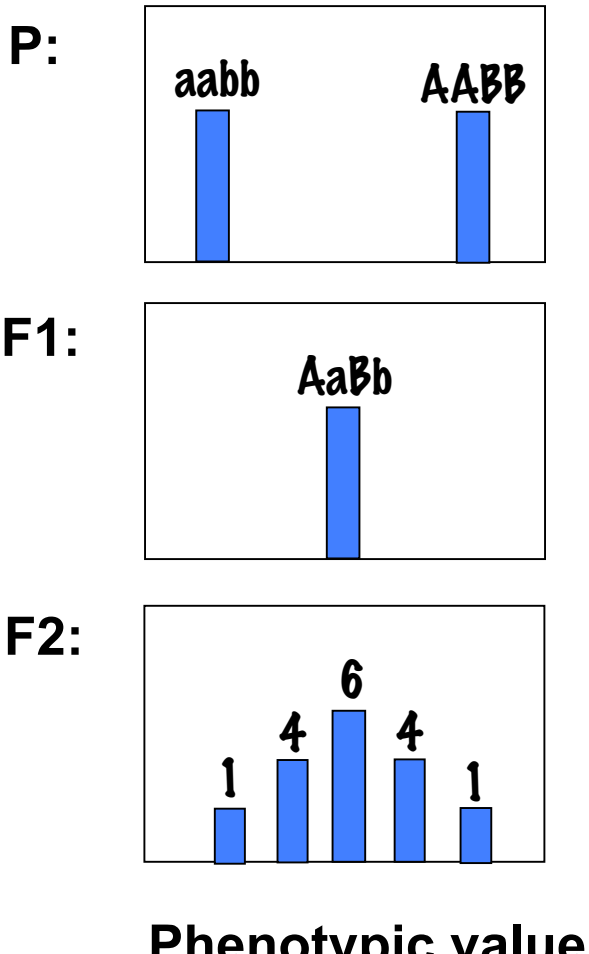
Genotype	Number of active alleles	Frequency	Phenotypic value
(1) AABB			
(2) AABb, (2) AaBB			
(4) AaBb + (1) AAbb + (1) aaBB			
(2) Aabb + (2) aaBb			
(1) aabb	0		

What Happens With Two Genes?

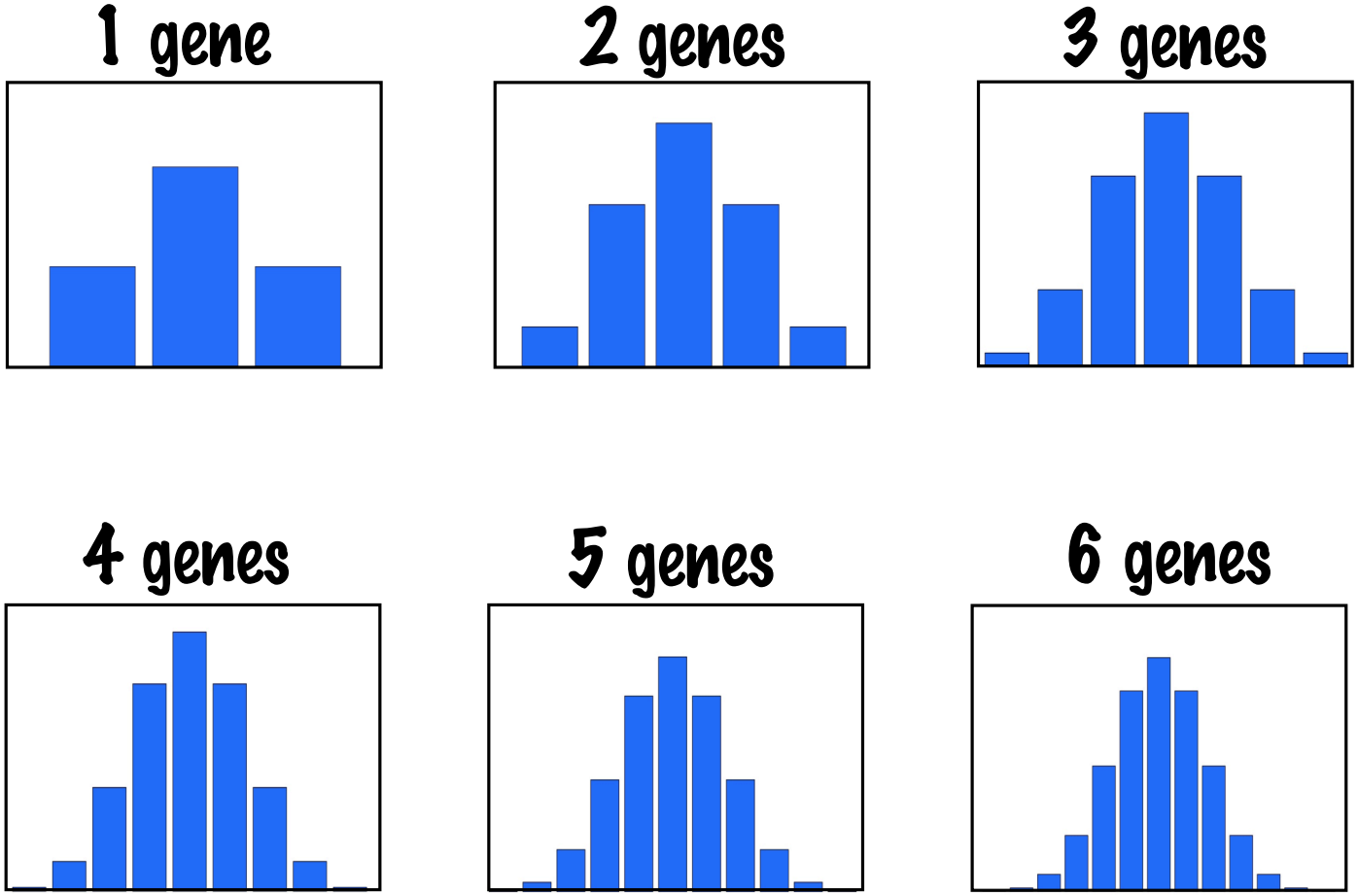
If we do a AaBb x AaBb cross we would expect the following genotypes and phenotypes in the progeny:

Genotype	Number of active alleles	Frequency	Phenotypic value
(1) AABB	4	$^{1}/_{16}$	$\mu + 4x$
(2) AABb, (2) AaBB	3	$^{4}/_{16}$	$\mu + 3x$
(4) AaBb + (1) Aabb + (1) aaBB	2	$^{6}/_{16}$	$\mu + 2x$
(2) Aabb + (2) aaBb	1	$^{4}/_{16}$	$\mu + x$
(1) aabb	0	$^{1}/_{16}$	μ

Graphically…



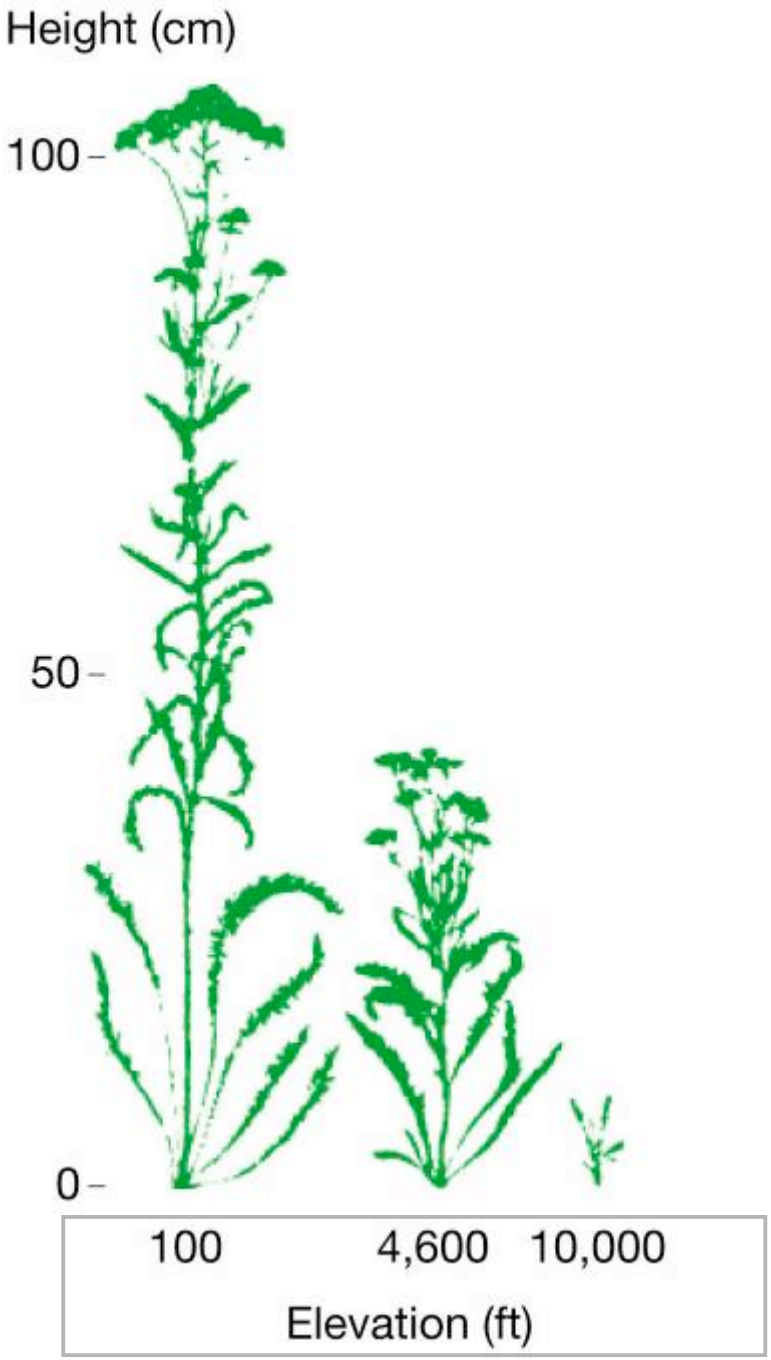
Phenotypic Distribution in F2 With Additional Genes



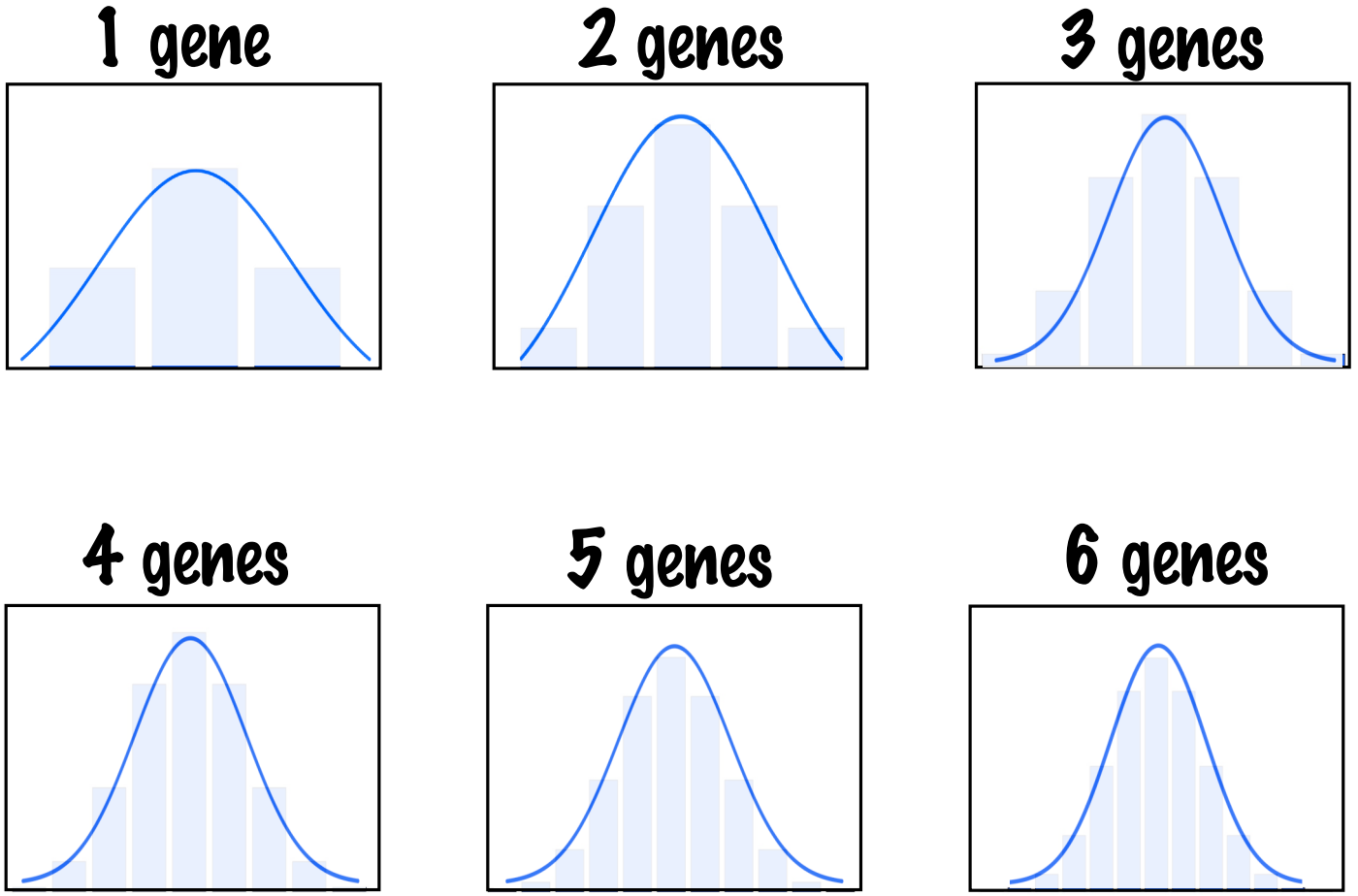
2n+1 phenotypic classes for n genes

Environment Also Contributes To Phenotypic Variation

Yarrow *plant (Achillea)*



Genetic + Environmental Variation = Quantitative Traits



Practice Question

Two average sized parents have three children. The first child is very short, the second child is very tall, and the third child is average sized.

(a) Explain the inheritance pattern of height in this pedigree. In particular, how is it possible for these parents to have both a very short and a very tall child?

(b)The parents decide to have a fourth child. Is it most likely to resemble the first, second, or third child?

Beyond The Basics

Weedon et al. (2008) performed a genome-wide association of adult height study in 13,655 individuals

Identified 20 QTL (quantitative trait loci) that influence adult height

Guess what percent total phenotypic variation these 20 loci explain

3% - or about 0.15% each!

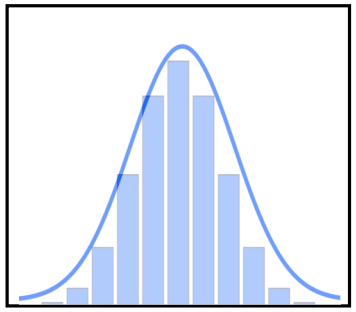
If height is 80% heritable and each variant explains 0.15% this suggests that genetic variation in > 500 genes influences height. Yikes...

Summary

1. Qualitative traits -> classify individuals

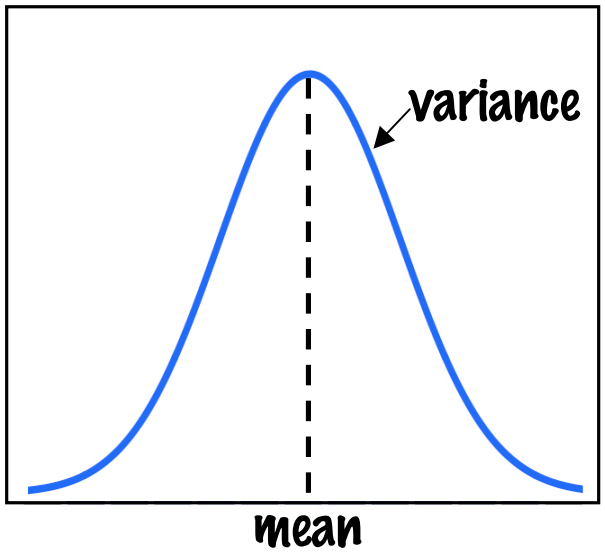
   Quantitative traits -> measure individuals

2. Quantitative traits arise from genetic variation at many loci (genes) and environmental variation



3. Mendelian ratios are not observed for quantitative traits - we need a different approach to study them!

How Do We Study Quantitative Traits?



Phenotypic variance: total variance of the population

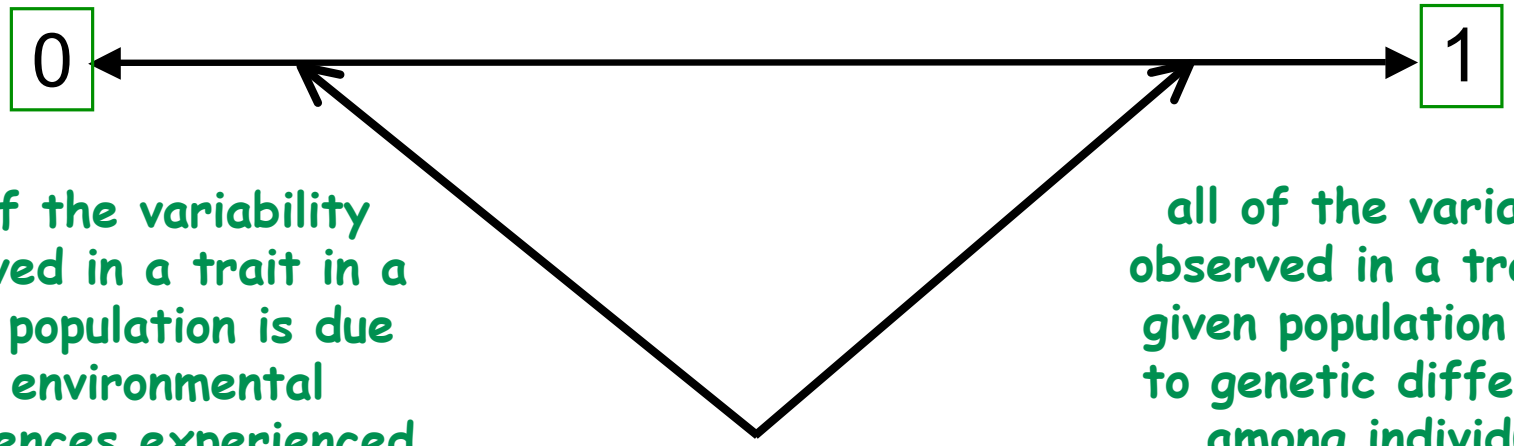
Phenotypic variance = Genetic variance + Environmental Variance

$$V_P = V_G + V_E$$

Separating Components of Variation

Heritability: the proportion of phenotypic variation among individuals in a population that is due to genetic variation

$$H^2 = \frac{V_G}{V_P} = \frac{V_G}{V_G + V_E}$$



all of the variability observed in a trait in a given population is due to environmental differences experienced among individuals

all of the variability observed in a trait in a given population is due to genetic differences among individuals

Heritability Practice Problem

A study was performed to estimate the heritability of human height. Heritability estimates were initially performed in children (average age 5 years old), and found to be 0.74. Heritability was estimated again in the same set of individuals when they were adults (average age 40 years old), and found to be 0.30. How can these results be explained?

$$H^2 = \frac{V_G}{V_P} = \frac{V_G}{V_G + V_E}$$

Heritability is the ratio of genetic variation to total phenotypic variation. Since the individuals have essentially the same amount of genetic variation throughout life, environmental variation must have increased later in life, thus reducing the estimated heritability.

What is Wrong With These Statements

1. My TA is really awesome. His/Her heritability for awesomeness must be really high.

   Heritability is a property of populations not individuals

2. The heritability for trait x is 0. Therefore, genetics must not be important for this trait.

   Heritability says nothing about whether genes influence a trait; only the extent to which genetic variation contributes to phenotypic variation

3. The heritability for a disease is 1. Therefore, attempts to modify disease risk through environmental interventions is pointless.

   An estimate of heritability only applies to the environment in which it was measured in; it could be entirely different in another environment.

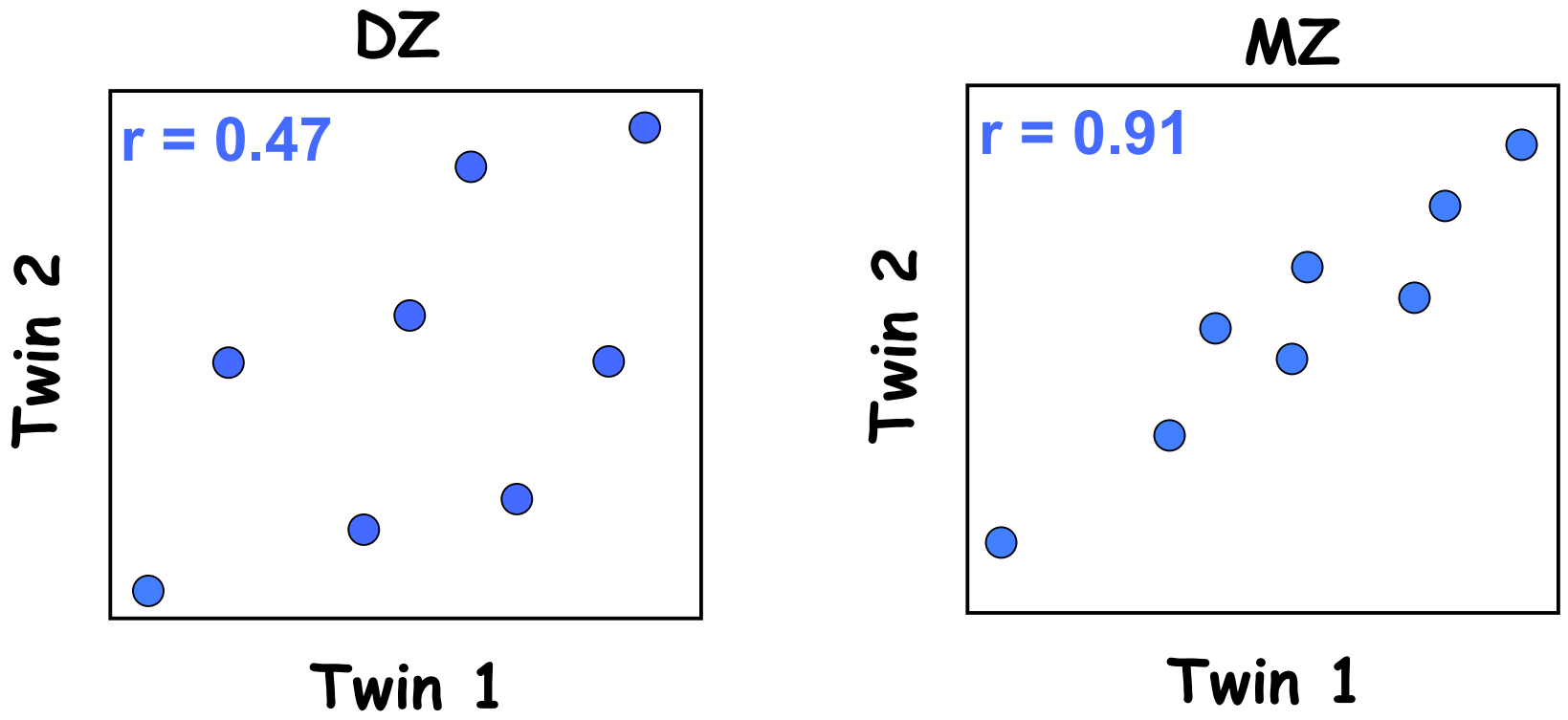
How Do We Estimate Heritability in Humans?

- From the resemblance among relatives
- The more similar relatives are for a phenotype the higher the heritability
- Twin studies are "best" study design:

Monozygotic (MZ) twins: share 100% of their genes; any variation due to environment

Dizygotic (MZ) twins: share 50% of their genes; variation due to both genetic and environmental variation

A Twin Study to Estimate the Heritability of Height



$$H^2 = 2(r_{MZ} - r_{DZ})$$

$$H^2 = 2(0.91 - 0.47)$$

$$H^2 = 0.88$$

Estimating heritability from twin studies

What are some potential problems of twin studies?

Heritability of Various Behavioral Phenotypes In Humans

Table 4.2 Correlations Between Identical Twins Reared Apart

Personality Trait	Twin Correlation
Sense of well-being	.49
Social potency	.57
Achievement orientation	.38
Social closeness	.15
Neuroticism	.70
Sense of alienation	.59
Aggression	.67
Inhibited control	.56
Low risk taking	.45
Traditionalism	.59
Absorption or imagination	.74
Average twin correlation	.54