Summer Institutes of Statistical Genetics, 2022

Module 2: INTRODUCTION TO GENETICS AND GENOMICS

Greg Gibson and Joe Lachance

Georgia Institute of Technology

Lecture 2: HERITABILITY

greg.gibson@biology.gatech.edu

http://www.cig.gatech.edu

Genotype and Phenotype

The genotype of an organism is the sequence of it's genes.

The phenotype of an organism the way it appears.

In general, genes are not deterministic. Genotypic variation among organisms specifies the information that, in combination with the environment, influences the phenotype.

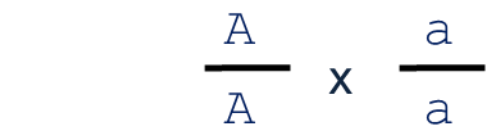
Genotype associations are mostly statistical biases, but nevertheless "causal"

Pleiotropy refers to the ability of single genes to influence multiple phenotypes.

Penetrance is the proportion of individuals with a genotype who have the phenotype / disease.

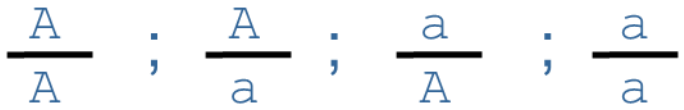
Expressivity is the degree / severity of the phenotype in affected individuals.

Mendelian Genetics



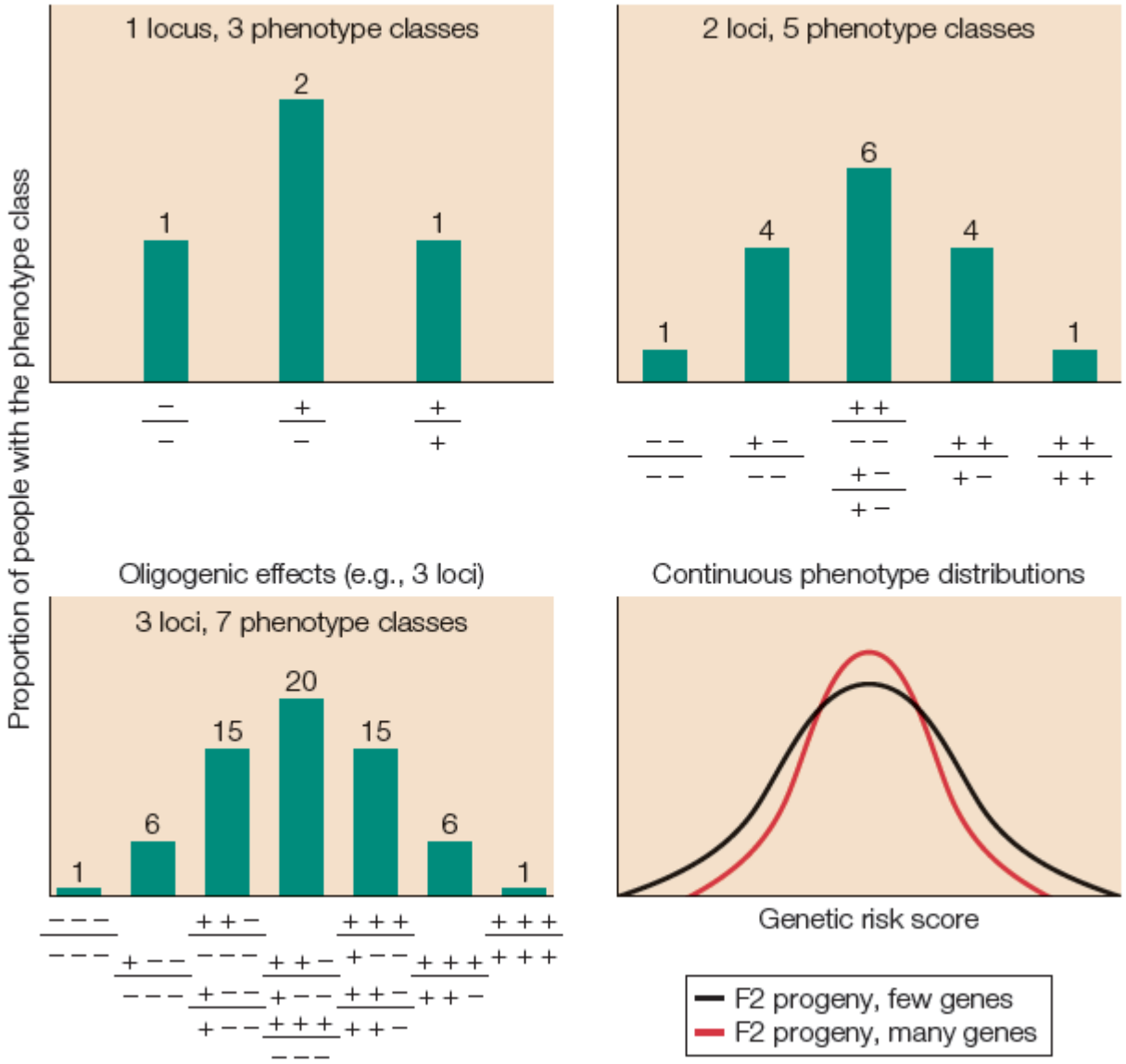
F0: Pure breeding parents

F1: Heterozygous offspring



F2: Mendelian proportions of Homozygotes + Heterozygotes

From Mendelian to Quantitative Genetics



Which of the following are highly heritable?

Height

Body Mass Index

Hair color

Your religion

Diabetes risk

Schizophrenia risk

Intelligence

Alcoholism

Athletic ability

3 Models of Human Disease

CDCV: Common Disease / Common Variant

The proposition that most disease susceptibility can be attributed to 10 to 20 loci, each of which explain around 5% of disease risk.

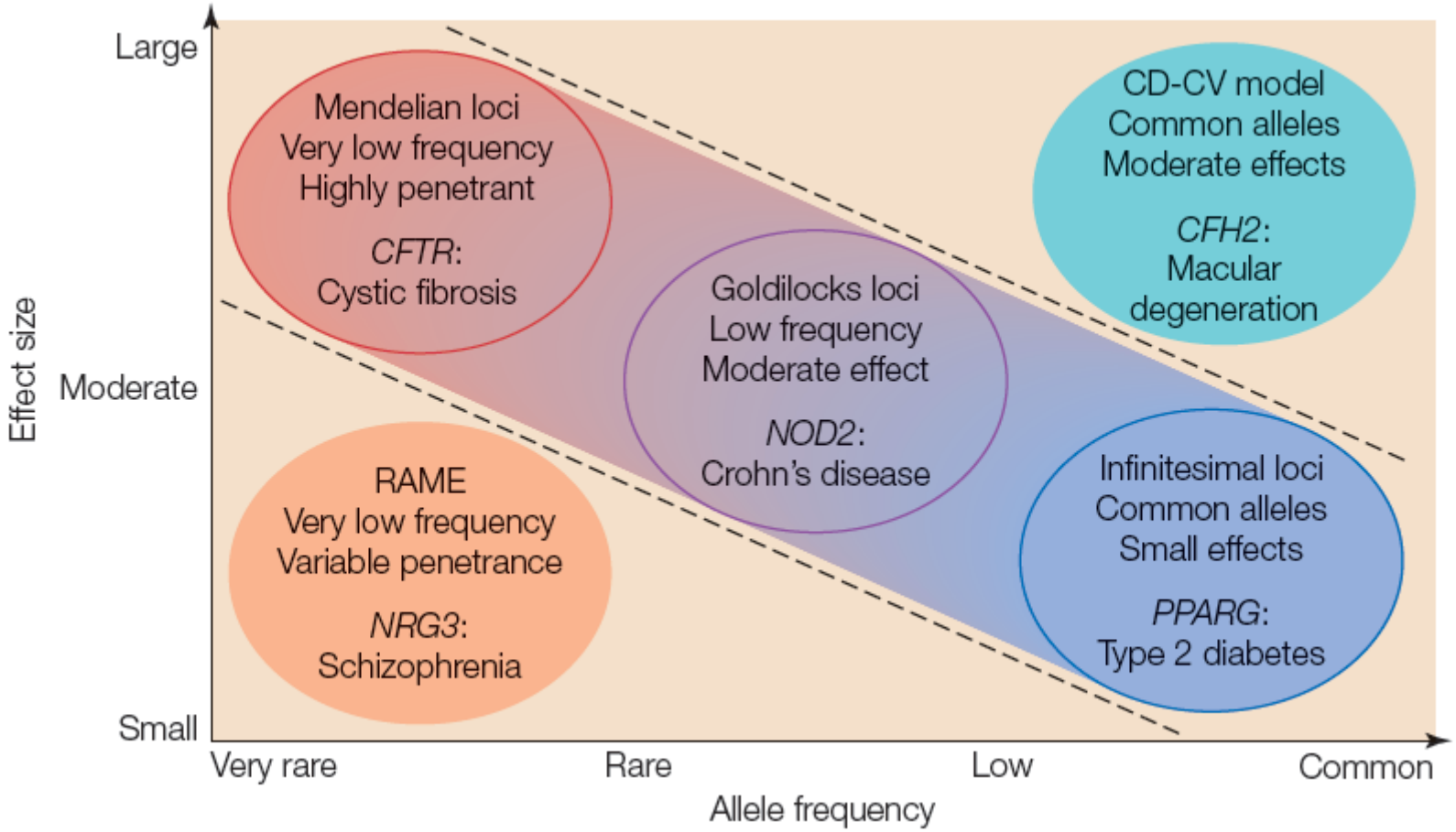
RAME: Rare alleles of Major Effect

The proposition that diseases are highly heterogeneous, with hundreds or thousands of rare mutations causing individual cases of disease.

Infinitesimal:

The proposition that we all carry thousands of very weak susceptibility alleles, and those unlucky enough to have too many are at highest risk, where rare variants or environmental triggers push us over the edge.

The Genetic Architecture of Complex Traits



Manolio et al (2009) *Nature* **461**: 747-753

Heritability

Heritability is the proportion of variance in a population that can be attributed to genotypic differences

$$h^2 = V_G/V_P \text{ where } V_P = V_G + V_E$$

The phenotypes may be discrete, such as disease status; categorical, such as number of digits; or continuous, such as height or a biochemical measure.

1. Heritability is not a statement about individuals.

A heritability of 50% for diabetes does not imply that half the reason why someone is diabetic is genetic, the other half environmental. Rather, it suggests that there would be half as much diabetes in the population if everyone was genetically identical.

2. Heritability is only a statement about a single population.

A heritability of 80% for height does not imply that most of the average difference in height between populations is due to genetic differences. Heritability estimates alone should not be used to draw inferences about genetic divergence between groups.

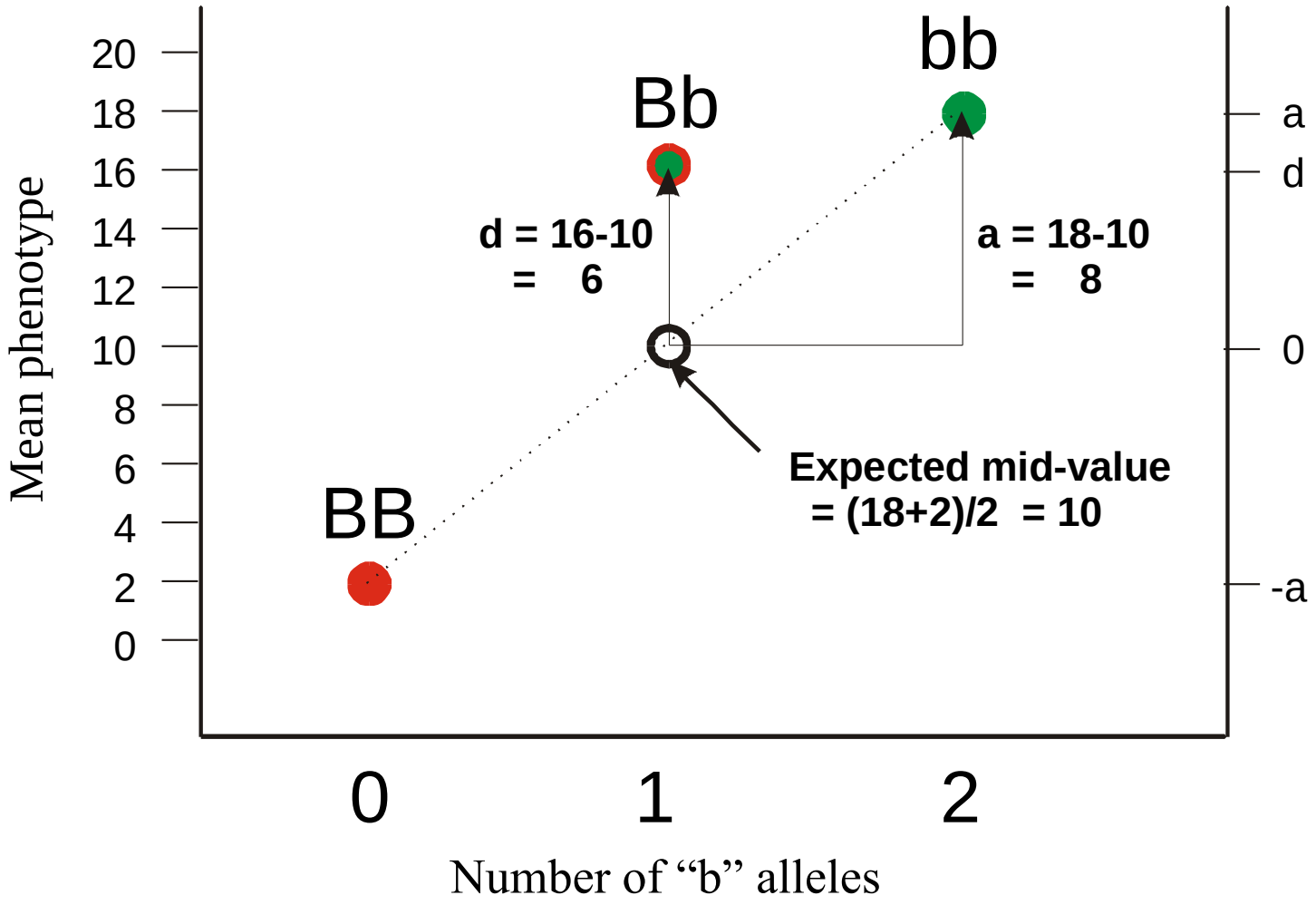
3. Heritability is not the same as inheritance.

Inheritance is the correspondence between children and their biological parents. It can be due to environmental, including cultural, factors that are shared by family members, or to effects. The only way to confidently interpret heritability is to actually measure the genotypic contribution.

4. Very low heritability does not imply very little genetic contribution.

It may either be due to relatively high environmental variance (hence, a large demominator V_P), or to an absence of variance in the genes that contribute. Many important genes, including drug targets, are not polymorphic and will only be discovered through other types of approach including model organism research.

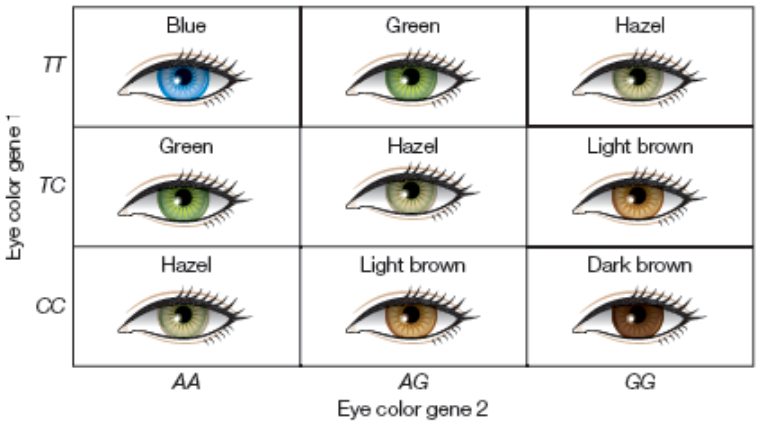
Dominance

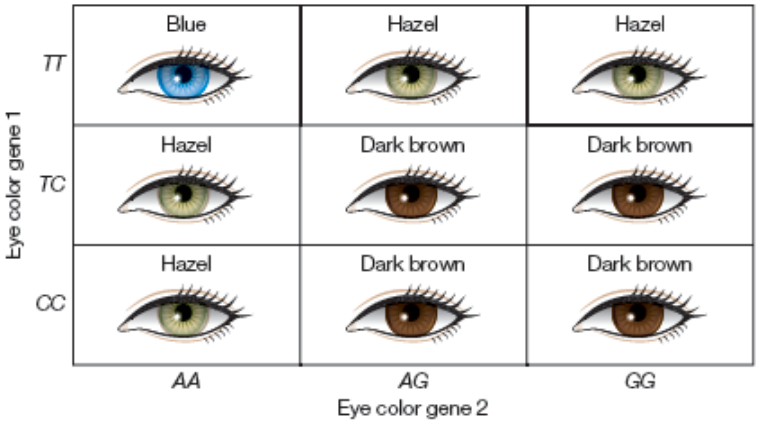

Mean phenotype
20
18
16
14
12
10
8
6
4
2
0
BB
Bb
bb
d = 16-10
= 6
a = 18-10
= 8
Expected mid-value
= (18+2)/2 = 10
a
d
0
-a
0
1
2
Number of "b" alleles

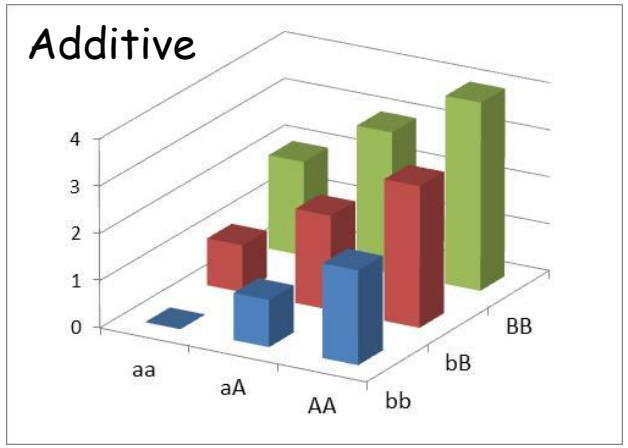
Narrow and Broad Sense heritability

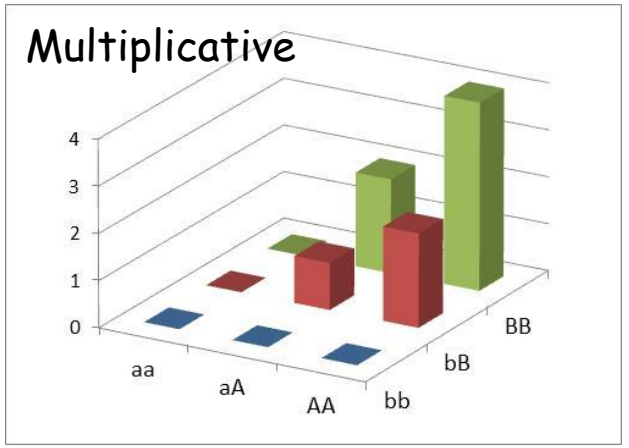
$$V_G = V_A + V_D + V_I + V_{G\times E}$$

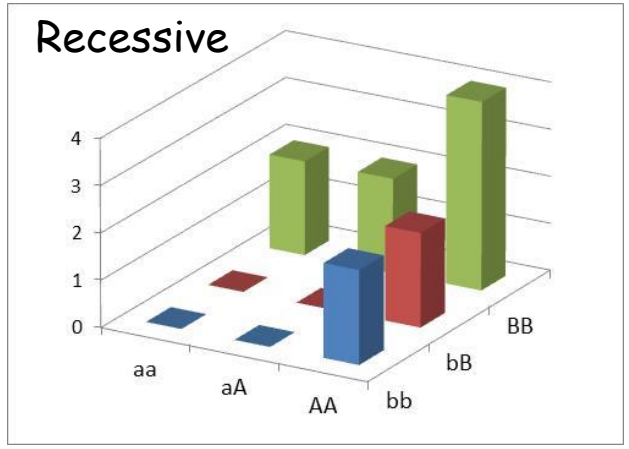
Narrow sense heritability is only the additive component whereas Broad sense heritability includes dominance, interaction and genotype-by-environment effects.

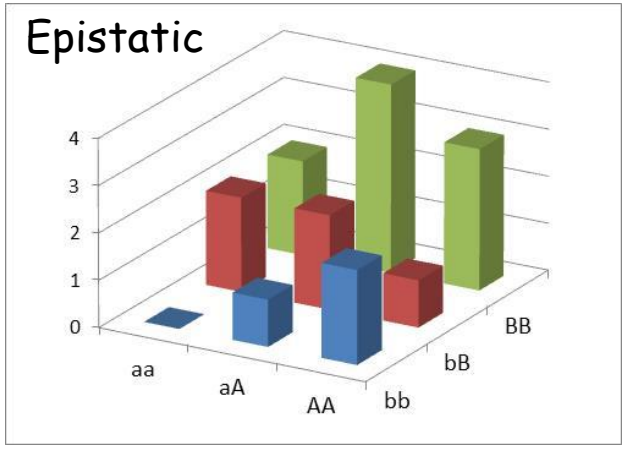






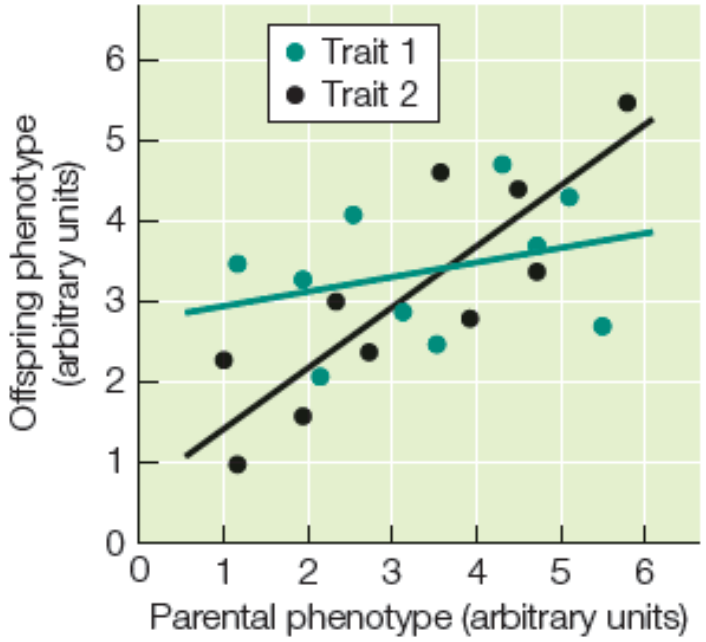




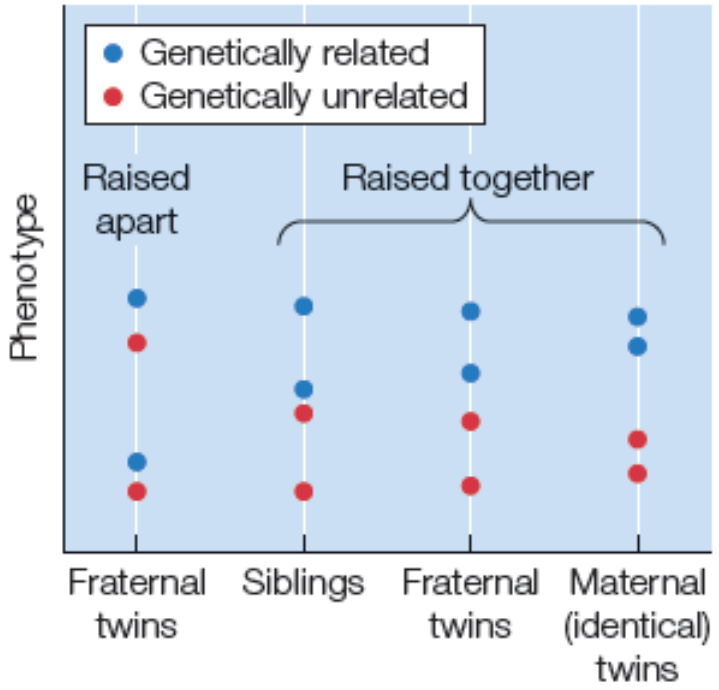
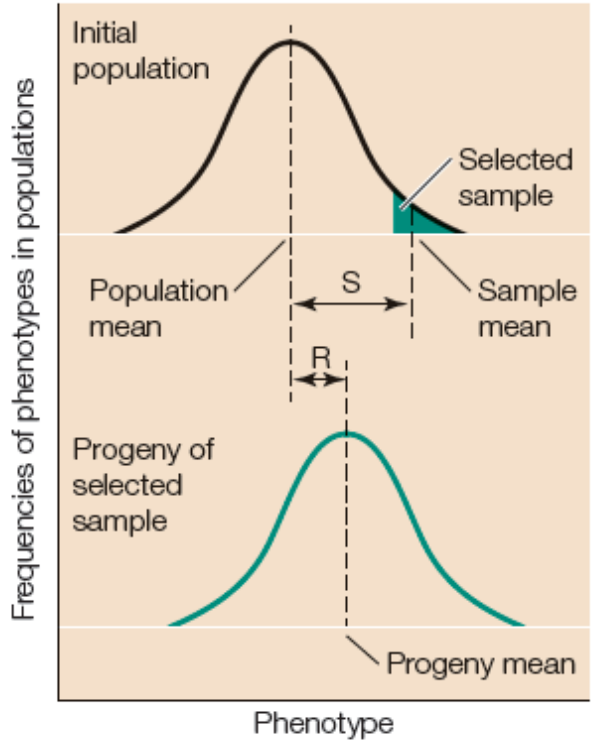


Estimating Heritability

(A) Parental-offspring regression



(B) Twin studies



(C) Realized heritability